Sleight (*135*) and Borgel, et al. (*7*) have demonstrated cardiovascular depressor reflexes in dogs elicited by nicotine stimulation of the surface of the left ventricle. Studies have been undertaken in dogs to determine the effect of beta-sympathetic receptor blockade by propranolol on the cardiac actions of nicotine. Westfall (*158*), Edmundowicz (*32*), Papacostas, et al. (*116*), Shanks (*131*) and Puri (*119*) have noted that propranolol can prevent the usual positive inotropic effects of nicotine or norepinephrine stimulation on the myocardium as well as the indirect beta dilator effects on peripheral vessels. This results proportionately in a greater increase in left ventricular afterload accompanied by a reciprocal decline of the velocity of myocardial fiber shortening (*129*). It was also noted that resulting unopposed alpha receptor activation by nicotine could lead to increased total peripheral resistance with impaired stroke volume and cardiac output. This is further evidence that catecholamines, the release of which is induced by smoking, intermediate the cardiovascular response to nicotine.

The effect of nicotine in single and repeated administrations was studied on the terminal vascular bed of the heart by Corsini, et al. (*27*). Results indicate that in dogs with intact coronary circulations, the single intravenous infusion of nicotine (150 ug./kg. body weight/minute) increased both the left ventricular capillary blood flow as well as the terminal vascular capacity; the chronic intramuscular administration (0.5 mg./kg. body weight given 3 times/day for 2 months), however, had no such effect. In contrast, in dogs with constriction of the coronary arteries, nicotine administration in either (single or repetitive doses) form resulted in a fall of capillary blood flow but an increase in the terminal vascular capacity. Capillary blood flow as measured in these studies represents a nutrient inflow to the myocardium. Nicotine administration resulted in an increase in both the velocity of myocardial shortening as well as the force of contraction, and these effects of nicotine are identical to those of norepinephrine. In addition, there was also an increase in the rate of left ventricular pressure rise (dp/dt) and a decline in left ventricular end-diastolic pressure (*121*).

Coleman, et al (*25*) studied isolated cat papillary muscles to determine the mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption. They found that norepinephrine does not increase the myocardial tissue oxygen demand unless contractility is increased, other factors being held constant. Norepinephrine is known to increase myocardial contractility.

Further studies (*49, 142*) on anesthetized open-chest dogs to determine the relative influences of changes in either the contractile state or in tension development on myocardial tissue oxygen consumption, indicate that both are significant factors. Basal oxygen requirements, activation energy, and the cost of contractile element shortening against a load appear to influence myocardial tissue oxygen consumption to a lesser degree.

Chidsey, et al. (*21, 22*) studied the relationship of norepinephrine to heart failure and the functional state of the human myocardium. They reemphasize the role of norepinephrine in altering myocardial fiber length and contractile status as demonstrated in human left ventricular papillary muscles removed from patients at the time of mitral valve replacement.

Ayres (*4*) has noted products of anaerobic cardiac metabolism in dogs made ischemic by exposure to carbon monoxide. These will be presented in a subsequent section of this chapter. Weissler, et al. (*156*), in experiments with isolated perfused rat hearts, have reported on the importance of glucose as a substrate for anaerobic metabolism of the heart subjected to anoxia for 30 minutes. When glucose was added to the anaerobic perfusate, the electrical and mechanical performance of the heart improved markedly, as did the recovery of the heart during the subsequent period of reoxygenation. Lactate production was fivefold greater in the glucose-supported anoxic heart than in the anoxic heart without glucose. In similar fashion, morphologic changes of the mitochondria and longitudinal tubules of the anoxic heart noted by electron microscopy, were averted by the inclusion of glucose in the perfusion fluid. This experiment suggests that glucose might help temporarily to prevent myocardial infarction, caused by relative myocardial anoxia, by providing a substrate for anaerobic cardiac metabolism.

(*135*) Sleight, P. A cardiovascular depressor reflex from the epicardium of the left ventricle in the dog. Journal of Physiology 173(3): 321-333, 1964.

(*7*) Borgel, D. H., Makin, G. S. Central and peripheral cardiovascular changes following chemical stimulation of the surface of the dog's heart. Cardiovascular Research 1(1): 58-70, 1967.

(*158*) Westfall, T. C., Cicolloni, P. B., Edmundowicz, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine 123: 174-179, 1966.

(*32*) Edmundowicz, A. C., Cicolloni, P. B., Perkins, K. E. Cardiovascular responses to cigarette smoke and nicotine in dogs following beta-adrenergic blockade with propranolol. (Abstract) Federation Proceedings 24: 713, March-April 1965.

(*116*) Papacostas, C. A., Reed, J. F. Influence of beta receptor blockade on certain cardiovascular actions of nicotine. Archives Internationales de Pharmacodynamie et de Therapie 164(1): 167-172, 1966.

(*131*) Shanks, R. G. The pharmacology of beta sympathetic blockade. American Journal of Cardiology 18(3): 338-346, September 1966.

(*119*) Puri, P. S., Alamy, D., Bing, R. J. Effect of nicotine on the contractility of the intact heart. Journal of Clinical Pharmacology, 1968. (In press)

(*27*) Corsini, G. C., Puri, P. S., Bing, R. J. Effect of nicotine on capillary flow and vascular bed of the heart in presence and absence of experimental coronary artery insufficiency. Federation Proceedings 27(2): 652, March-April 1968.

(*121*) Puri, P. S., Bing, R. J. Influence of cardiovascular drugs on the force-velocity relation of the intact heart. The Physiologist 10(3): 255, August 1967.

(*25*) Coleman, H. N., Sonnenblick, E. H., Braunwald, E. Mechanism of the norepinephrine-induced stimulation of myocardial oxygen consumption as studied in the isolated cat papillary muscle. Circulation (Supplement III) 36(4): 80, October 1967.

(*49*) Graham, T. P., Jr., Covell, J. W., Sonnenblick, E. H., Ross, J., Jr., Braunwald, E. Control of myocardial oxygen consumption: Relative influence of contractile state and tension development. Journal of Clinical Investigation 47: 375-385, 1968.

(*142*) Taylor, R. R., Cingolani, H. E., Graham, T. P., Clancy, R. L. Myocardial oxygen consumption: left ventricular fibre shortening and wall tension. Cardiovascular Research 1: 219-223, 1967.

(*21*) Chidsey, C. A., Braunwald, E., Morrow, A. G. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. American Journal of Medicine 39(3): 442-451, September 1965.

(*22*) Chidsey, C. A., Sonnenblick, E. H., Morrow, A. G., Braunwald, E. Norepinephrine stores and contractile force of papillary muscle from the failing human heart. Circulation 33(1): 43-51, January 1966.

(*4*) Ayres, S. M. Personal communication. March 1968.

(*156*) Weissler, A. M., Kecker, F. A., Baba, N., Scarpelli, D. G., Leighton, R. F., Gallishaw, J. K. Role of anaerobic metabolism in the preservation of functional capacity and structure of anoxic myocardium. Journal of Clinical Investigation 47: 403-416, 1968.

Experimental Studies on the Heart. The lengthy discussion on cardiovascular response to smoking and nicotine which started in the preceding page and continued to the next page does not relate directly to the question of cigarette smoking. Most of the cited references are on catecholamines, carbon monoxide and hypoxia. There are only two references on cigarette smoke: (158) Westfall et al. and (32) Edmundowicz et al. relating to the release of catecholamines but the amount of cigarette smoke administered was excessive, since there was a significant rise in blood pressure (119 to 176) and slowing of the heart rate. There is no cited reference that catecholamines can be released by administration of ordinary amounts of cigarette smoke which does not influence blood pressure.

CARDIOVASCULAR RESPONSES TO CIGARETTE SMOKE AND NICOTINE IN DOGS FOLLOWING β-ADRENERGIC BLOCKADE WITH PROPRANOLOL (I.C.I. 45,520). A. C. Edmundowicz, P. A. Cipollone, and W. F. Penrod. West Virginia Univ. Sch. of Med., Morgantown, W. Va.

Eight anesthetized dogs were made to inhale smoke from cigarettes through a cuffed endotracheal tube; respirations were either spontaneous or controlled by a pump respirator. Smoking caused an increase in mean arterial pressure (A.P.) from 119 to 176 mm. Hg, a decrease of 41% in heart rate (H.R.), and increases of 72% in stroke volume (S.V.) and 34% in cardiac output (C.O.) (all mean values). Mean levels of epinephrine (E) and norepinephrine (N) in blood from the high inferior vena cava (I.V.C.) increased from <0.2 to 113 and from <0.2 to 23 γ/L respectively. Similar responses followed I.V. injections of nicotine. After β-adrenergic blockade with 0.2 mg./kg. propranolol I.V., smoking decreased H.R. by 22%, S.V. by 9%, and C.O. by 34%. Mean A.P. increased from 110 to 196 mm. Hg and several dogs developed transient left ventricular failure. Mean levels of E and N in the high I.V.C. increased from <0.2 to 145 and from <0.2 to 20 γ/L. Responses to nicotine following blockade were similar. Conclusion: β-adrenergic blockade by propranolol does not modify the release of catecholamines from the adrenal gland of dogs in response to smoking and nicotine; unmasking of α receptor activity causes severe hypertension and compromises left ventricular function. (Supported by USPHS Grant 07758-02).

The other experiments cited relate to nicotine. The significance of measurement of nutrient blood flow was not mentioned. Nicotine increases nutrient flow in a dog with coronary constriction indicating that there is adequate blood flow in the ischemic area following nicotine injection.

The isolated perfused rat heart was also studied by Brachfeld, et al. (12) to determine the effects of nicotine on lysosomal, mitochondrial, and supernatant enzyme systems of the myocardium. They suggested that nicotine toxicity may be expressed in terms of damage to the lysosomal membrane and the cell wall. Shibata, et al. (132) studied the action of nicotine on the transmembrane potential and contractility of isolated rat atria. They suggest that while nicotine may influence membrane electrodynamics, there may also be a direct action on the contractile mechanism of the cardiac muscle cell by changing the duration of the action potential, which implies alterations in potassium fluxes.

Nicotine-induced changes, in dogs, in action potentials and conduction depression, with enhancement of Purkinje fibre "automaticity," may lead to the development of ventricular fibrillation (50). Post myocardial infarction dogs were much more sensitive to the administration of nicotine, as measured by electrocardiographic changes, than were normal dogs, especially in the acute stage of myocardial infarction (6). Webb, et al. (134) state that changes in fibrillation thresholds after cigarette smoking noted in dogs, by analogy, "may have relevance to the higher incidence of coronary deaths without increased incidence of angina in cigarette smokers."

Studies in Humans

The 1967 report noted that sudden death from previously undetected coronary heart disease appeared to occur frequently among cigarette smokers. Kuller (94) showed in a study of sudden death in Baltimore that arteriosclerotic heart disease was a major cause (61.4 percent) of death. No smoking histories were recorded. Luke, et al. (99) reviewed 275 consecutive autopsied cases of sudden unexpected death from natural causes, in individuals age 20 to 45 years, and noted that asymptomatic coronary artery disease comprised 25 percent of the causes of sudden death. Again, no smoking data were taken. Data pooled from 10 studies available to Burch, et al. (17), indicated that cardiovascular disease accounted for 51 percent of 8,151 adult sudden deaths.

Present clinical evidence indicates that ventricular asystole or fibrillation may be the mechanism of sudden cardiovascular death in most cases. It is known that hypoxia, hypercapnia, ischemia, electrolyte disturbances, and increased catecholamine activity all can predispose to ventricular fibrillation. From available physiological evidence noted elsewhere in this and the bronchopulmonary chapter, and also in the 1967 Report, it would appear that smoking can directly or indirectly contribute to the development of these predisposing conditions. It is well accepted clinically that ventricular, nodal, or atrial premature contractions can be increased or induced by cigarette smoking, as well as by other factors, and can be reduced by the cessation of cigarette smoking in both normal and ischemic hearts. These premature contractions are frequently precursors of their respective tachycardias. Also, a person with an acute or impending myocardial infarction subjected to the sympathoadrenal effect of smoking could more readily develop a fatal arrhythmia (75). The relationship of smoking to cardiac arrhythmias must be studied further to determine more exactly both the physiology and the mechanisms involved in sudden deaths from cardiovascular disease.

Kerrigan, et al. (74) studied cardiac output in both smokers and nonsmokers who had no evidence of coronary heart disease and found rises in cardiac output in response to exercise and to cigarette smoking separately and then in combination. They note that the total increase in cardiac output appears to be the sum of the exercise and the smoking effects. Smoking may create an additional myocardial tissue oxygen demand above and beyond the demand attributable to exercise.

Moses, et al. (105) reported that pretreatment of healthy normals with glucose blocks the increased cardiac output response to cigarette smoking by inhibiting the increases in stroke volume but not heart rate.

(12) Brachfeld, N., Kuehn, P., Kawade, M., Oran, E. Nicotine mediated release of myocardial cell and lysosomal enzymes. Annals of Internal Medicine 68(5): 1031, May 1967.

(132) Shibata, S., Hollander, P. H., Webb, J. L. Effect of nicotine on the transmembrane potential and contractility of isolated rat atria. Experientia 24(3): 236-237, 1968.

(50) Greenspan, K., Knoebel, S. B., Fisch, C. Effects of nicotine upon human and canine cardiac action potential and contractile state. (Abstract) The Project for Research on Tobacco and Health 1964-1968. American Medical Association Education and Research Foundation, June 1968. Pp. 24-25.

(6) Bellet, S., Kershbaum, A., Meade, R. H., Jr., Schwartz, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. American Journal of the Medical Sciences 201(1): 40-51, January 1941.

(134) Webb, W. R., Wall, S. D., Sproa, W. L. Cigarette smoke and fibrillation threshold in dogs. Clinical Research 16(1): 74, January 1968.

(94) Kuller, L., Lilienfeld, A. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. Circulation 34: 1056-1063, December 1966.

(99) Luke, J. L., Halpern, M. Sudden unexpected death from natural causes in young adults. A review of 275 consecutive autopsied cases. Archives of Pathology 85(1): 10-17, January 1968.

(17) Burch, G. E., DePasquale, N. P. Sudden, unexpected, natural death. American Journal of the Medical Sciences 249: 89-97, January 1965.

(75) Kershbaum, A. Personal communication. March 1968.

(74) Kerrigan, R., Jain, A. C., Doyle, J. T. The circulatory response to cigarette smoking at rest and after exercise. American Journal of the Medical Sciences 255: 113-119, February 1968.

(105) Moses, D. C., Powers, D., Soloff, L. A. Glucose blockade of the increase in stroke volume produced by smoking. Circulation 29(6): 830-834, June 1964.

Sudden Deaths - The incorrect statement in the 1967 report on sudden death is discussed in page 360 (a). The additional references relating to sudden death have no smoking data but contain information of risk factors which contribute to sudden death. For instance (94) Kuller and Lilienfeld reported that approximately two-thirds of coronary deaths had a history of at least one of the following: diabetes, hypertension and cerebrovascular disease, and heart disease. The relevant table from the article is as follows:

Table 8

Distribution of Arteriosclerotic Heart Disease Deaths by Race, Sex, and Number and Percentage with a History of Heart Disease or Several Other Cardiovascular Diseases (CVD)

Race & sex	Category	Total deaths	History of heart disease		History of diabetes		History of hypertension		No history of at least one disease or CVD	
			No.	%	No.	%	No.	%	No.	%
WM	Sudden	392	209	53.3	46	11.7	93	23.7	120	32.1
	Not sudden	193	133	68.9	35	18.1	54	28.0	—	—
WF	Sudden	89	39	43.8	7	7.9	37	41.6	38	42.7
	Not sudden	76	49	64.5	29	38.2	47	61.8	—	—
NM	Sudden	114	64	56.1	16	14.0	29	25.4	37	32.5
	Not sudden	60	33	55.0	14	23.2	20	33.0	—	—
NF	Sudden	71	27	38.0	7	9.9	26	36.6	30	42.3
	Not sudden	52	34	65.4	17	32.7	15	28.8	—	—
Total	Sudden	666	339	50.9	76	11.4	185	27.8	231	34.7
	Not sudden	381*	249	65.3	95	24.9	136	35.7	—	—

*Excludes 51 not-sudden deaths when the patient had been admitted to the hospital with a noncardiovascular disease and subsequently had a new coronary event in the hospital.

Frankl, et al. (42) noted that after 5 normal male chronic smokers were given propranolol, cigarette smoking caused a significant increase in systemic blood pressure and a significant decrease in cardiac output. Thus cigarette smoking after propranolol administration may be especially hazardous. Yamamoto noted similar results (160).

Sen Gupta, et al. (130) studied 11 ischemic cardiac patients and 14 healthy controls for abnormal ECG changes after smoking one cigarette and noted specific or nonspecific changes in almost all of the cardiac patients as compared to few changes in the healthy smokers and no abnormalities in the healthy nonsmokers. Pentecost, et al. (117) studied the acute effects of cigarette smoking in patients with angina or post-myocardial infarction as compared with normal controls. Normal men and those with angina in the absence of infarction behaved similarly with an increase in pulse rate, mean pressure, stroke volume, and cardiac output. The majority of the patients among the post-myocardial infarction group showed a marked fall in stroke volume and cardiac output while smoking. In another study (43) to evaluate the interrelationship of smoking and exercise effects on cardiac output, a fall in cardiac output that occurred in some post-infarction coronary patients as a result of smoking alone was noted. Also noted were decreases in cardiac output after smoking and exercising as compared to post-exercise cardiac output in the same patients before they smoked.

Starr (139) suggests that the ballistocardiographic (BCG) findings in cardiac disease and after cigarette smoking may provide valuable information about the rate of acceleration of myocardial contractile velocity that cannot be determined by studying cardiac output or stroke volume alone. A diseased heart has a slower accelerative rate of contraction. BCG abnormalities have frequently been related to cigarette smoking in subjects with or without heart disease, including angina pectoris. The BCG findings of Jackson, et al. (68) indicate that cigarette smoking itself may have acute and chronic harmful effects on myocardial function, since duration of smoking was also correlated with certain abnormalities.

Gazes, et al. (47), Braunwald, et al. (13), and Klensch, et al. (91) have found higher plasma norepinephrine levels in coronary patients at rest and after smoking as compared to normals. Kershbaum, et al. (77) have reported that the rise in free fatty acids after cigarette smoking is also greater in patients with coronary heart disease, probably due to an enhanced norepinephrine response.

Burch, et al. (16) also stress the importance of the action of norepinephrine on the venous vascular system. "Greater than 70% of the blood volume is contained within the systemic venous system and a 10% reduction in venous capacity would result in the sudden shifting of 350 ml. of blood (assuming a blood volume of 5 L.) centrally into the pulmonary veins and atria. In the presence of a diseased left ventricle, such a sudden increase in central blood volume may result in acute left ventricular failure" (17). (Additional cardiopulmonary considerations are noted in the bronchopulmonary disease chapter of this Report).

Human Myocardial Tissue Function in Relation to Anoxia and to Carbon Monoxide

Likoff, et al. (96) suggest that an oxygen-diffusion impairment or inappropriate oxygen utilization at the myocardial microcirculatory or cellular level could be responsible for the anginal symptoms and ECG signs of apparent myocardial ischemia in the presence of adequate arterial saturation and patent coronary arteries by coronary arteriography. Ayres (7) and Eliot (57) suggest that these mechanisms may be related to the carbon monoxide effect and abnormal hemoglobin function.

In addition to a review of the coronary circulation as related to myocardial ischemia and angina pectoris, Elliott, et al. (35) studied zonal myocardial ischemia (60) by ECG, coronary angiography and regional lactate metabolism in 50 patients with proven coronary heart disease. They found that the ECG findings could be normal even when severe coronary disease was present with myocardial production of lactate. The regional lactate pattern was very helpful in determining the location of myocardial ischemia and significant coronary artery lesions.

(42) Frankl, W. S., Soloff, L. A. The hemodynamic effects of propranolol hydrochloride after smoking. American Journal of the Medical Sciences 254(5): 623–628, November 1967.

(160) Yamamoto, T. The effect of propranolol on the haemodynamic changes caused by cigarette smoking. Japanese Circulation Journal 31(12): 1953. December 1967.

(130) Sen Gupta, A. N., Ghosh, B. P. Observations on some cardiovascular and biochemical effects of tobacco smoking in health and in ischaemic cardiacs. Bulletin of the Institute of Post-Graduate Medical Education and Research 9(2): 45–57, April 1967.

(117) Pentecost, B., Shillingford, J. The acute effects of smoking on myocardial performance in patients with coronary arterial disease. British Heart Journal 26: 422–429, 1964.

(43) Frankl, W. S., Winters, W. L., Soloff, L. A. The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction. Circulation 31(1): 42–44, January 1965.

(139) Starr, I. The place of the ballistocardiogram in a Newtonian cardiology: and the new light it sheds on certain old clinical problems. Proceedings of the Royal Society of Medicine 60: 1297–1306, December 1967.

(68) Jackson, D. H., Orpeman, A., Mitchell, R. E., Gravdiel, A. Factors contributing to the ballistocardiographic waveform in healthy middle-aged men. American Journal of Cardiology 20(4): 531–540, October 1967.

(47) Gazes, P. C., Richardson, J. A., Wood, E. F. Plasma catecholamine concentrations in myocardial infarction and angina pectoris. Circulation 19(5): 657–661, May 1959.

(13) Braunwald, E., Chidsey, C. A., Harrison, D. C., Gaffney, T. E., Kahler, R. L. Studies on the function of the adrenergic nerve endings in the heart. Circulation 28(5): 958–969, November 1963.

(91) Klensch, H., Speckmann, K., Mattfeld, F. W., Meyer, J. D. Der Plasma-Noradrenalinspiegel bei Koronarkranken in Ruhe und im Nikotin-Stress. Zeitschrift fur Kreislaufforschung 56(12): 1164–1169, December 1967.

(77) Kershbaum, A., Bellett, S., Caplan, R. F., Feinberg, L. J. Effect of cigarette smoking on free fatty acids in patients with healed myocardial infarctions. American Journal of Cardiology 10(2): 204–208, August 1962.

(16) Burch, G. E., DePasquale, N. P. Hematocrit, viscosity and coronary blood flow. Diseases of the Chest 48(3): 225–232, September 1965.

(96) Likoff, W., Segal, B. L., Kasparian, H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. New England Journal of Medicine 276(19): 1063–1066, May 11, 1967.

(57) Eliot, R. S., Beatt, G. S. Personal communication. April 1968.

(35) Elliott, W. C., Goglin, R. The coronary circulation, myocardial ischemia, and angina pectoris. Modern Concepts of Cardiovascular Disease 35(10): 111–116, October 1966.

(60) Herman, M. V., Elliott, W. C., Goglin, R. An electrocardiographic, arteriographic, and metabolic study of zonal myocardial ischemia in coronary heart disease. Circulation 45(5): 831–846, May 1967.

Exercise and Smoking in Post-Infarction Patients. The statements relating to (43) Frank et al. are incorrect. A fall in output was noted in 2 patients (-2 and -18%) and a rise in 6. The authors state "Smoking failed to produce the striking increase in output seen in young, healthy, habitual smokers." Furthermore, exercise and smoking caused an increase in output less than that seen in pre-smoking state. The Results and Summary are as follows:

Table 1

Findings before Smoking

Patient	Age	SA	Rest CO	Rest CI	Rest SV	Rest HR	Exercise CO	Exercise CI	Exercise SV	Exercise HR
S.C.*	64	1.55	2.84	1.84	50	57	4.52	2.92	54	84
W.E.*	62	1.90	3.82	2.04	57	66	5.10	2.71	57	90
E.F.*	53	1.56	3.85	2.46	64	60	6.88	4.41	82	84
C.C.*	69	1.51	2.55	1.67	35	72	4.04	2.67	46	87
M.H.*	55	1.64	2.69	1.64	45	60	3.62	2.20	38	96
A.J.*	48	1.92	3.83	1.99	71	54	7.87	4.08	82	96
A.L.†	56	1.99	3.50	1.76	56	63	7.66	3.85	91	84
F.L.†	68	1.75	3.44	1.97	60	57	5.44	3.11	60	91

* Chronic smokers.

† Nonsmokers.

SA, surface area in M^2; CO, cardiac output in L./min.; CI, cardiac index in L./min./M^2; SV, stroke volume in ml.; HR, heart rate in beats/min.

Table 2

Findings after Smoking

Patient	Rest CO	Rest %Δ	Rest CI	Rest %Δ	Rest SV	Rest %Δ	Rest HR	Exercise CO	Exercise %Δ	Exercise CI	Exercise %Δ	Exercise SV	Exercise %Δ	Exercise HR
S.C.*	2.78	−2.1	1.79	−3.2	44	−12.0	63	3.93	−12.6	2.55	−12.6	42	−22.2	93
W.E.*	4.10	+7.3	2.20	+7.8	52	−8.8	78	5.90	+15.7	3.10	+14.4	58	+1.75	102
E.F.*	4.10	+6.5	2.63	+6.9	57	−10.9	72	5.52	−19.8	3.54	−19.0	68	−17.0	81
C.C.*	4.68	+45.5	3.10	+46.1	46	+23.9	102	4.45	+10.1	2.95	+10.5	48	+4.4	93
M.H.*	2.19	−18.5	1.33	−18.8	37	−17.7	60	—	—	—	—	—	—	—
A.J.*	4.44	+15.9	2.31	+16.0	55	−22.5	81	7.47	−5.1	3.89	−4.6	57	−34.1	132
A.L.†	4.03	+15.1	2.02	+14.9	58	+3.6	63	7.94	+3.6	3.99	+3.6	95	+4.4	84
F.L.†	3.96	+15.1	2.26	+14.7	55	−12.0	72	6.48	+19.1	3.70	+19.0	58	−3.3	111

*Chronic smokers.

†Nonsmokers.

CO, cardiac output in L./min.; CI, cardiac index in L./min./M^2; SV, stroke volume in ml.; HR, heart rate in beats/min.; %Δ, Per cent change from nonsmoking state.

Summary

Smoking by subjects with healed myocardial infarction, in contrast to its effects on the normal subject, fails to provoke an increase in cardiac output or in stroke volume. On the other hand, smoking does increase the heart rate in subjects with healed myocardial infarction. This dissociation between the effect on heart rate and on cardiac output and stroke volume, which was also noted in the healthy subject pretreated with glucose, indicates that increase in heart rate is mediated by different factors than those that increase stroke volume and cardiac output.

In studies of coronary patients exposed to relatively low levels of carbon monoxide, Ayres (7) has reported that myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting the presence of anaerobic metabolism. These data support his previous findings noted in the 1967 report that carboxyhemoglobin can interfere with oxygen delivery to the myocardium to the degree that relative myocardial anoxia can occur. The shift to anaerobic cardiac metabolism, which is relatively ineffective as a source of energy, indicates the presence of myocardial anoxia, and should be regarded as a warning sign. In these same experiments Ayres has noted that the myocardial oxygen extraction is decreased in response to carbon monoxide inhalation, and thus has further demonstrated the relationships of carbon monoxide with relative myocardial anoxia and anaerobic myocardial metabolism. The shift to the left of the hemoglobin-oxygen dissociation curve, describing the decreased ability of hemoglobin to release oxygen at the tissue level, is directly related to increased carboxyhemoglobin levels.

The animal experiments of Weissler (*159*), noted in the previous section, suggest that glucose might possibly help to temporarily prevent myocardial infarction from relative myocardial anoxia, by providing a substrate for anaerobic metabolism. Since myocardial ischemia may be caused not only by complete coronary arterial obstruction, but also by increased myocardial tissue oxygen demand above and beyond available oxygen supply, it would be important to know whether cigarette smokers have more products of anaerobic myocardial metabolism than do nonsmokers.

Eliot (33) has noted apparent hemoglobin abnormalities in patients with signs of myocardial ischemia or acute necrosis, and in smokers as compared to controls. However, he suggests that there are other hemoglobin abnormalities also present besides the well documented carboxyhemoglobin abnormalities associated with the carbon monoxide effect of cigarettes. Some reverted to normal hemoglobin status after stopping smoking.

Anomalous hemoglobin-oxygen dissociation was noted in "heavy" cigarette smokers (more than one pack per day) without known coronary heart disease. In experiments where the amount of cigarette smoking was controlled, there appeared to be a threshold effect: more than 12 cigarettes per day caused this anomalous dissociation to occur (53). Birnstingl (9) reports finding an increased hemoglobin affinity for oxygen in smokers, which does not appear to be explained solely by the increased carboxyhemoglobin levels in smokers.

Research to further study the interrelationships of carbon monoxide to the myoglobin of heart muscle should be performed because it is possible that carbon monoxide may replace oxymyoglobin with carboxymyoglobin and disturb the oxygen-dissociation phenomena of myoglobin (88, 126, 159). The limitations of blood supply and the high energy output of heart muscle as compared to skeletal muscle may make the myoglobin impairments by carbon monoxide of possible etiologic importance in cigarette smoking and heart disease.

Hydrogen cyanide appears to be rapidly converted to thiocyanates by the body, but the absorption by the lung of cyanide from cigarette smoke might possibly result in higher serum cyanide levels in the coronary arteries than in the systemic circulation. As noted in the 1964 Report, the cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in nonsmokers and relative differences in urinary excretion are even more pronounced. Cytochrome oxidase is very important in cellular respiration of all body cells. In view of the extremely high myocardial cellular needs for aerobic metabolism, it is possible that the cyanide ion inactivation of cytochrome oxidase also can occur in myocardial cells and be of critical importance, especially in light of other risk factors such as impaired coronary blood flow, the carbon monoxide effect, and the known increases in myocardial tissue oxygen demand caused by the smoking/nicotine-induced catecholamine release. Further research is needed to determine whether or not cyanide ions in concentrations equivalent to those found in cigarette smokers, have a harmful effect on the myocardium, in terms of both acute and chronic exposures.

(33) Eliot, R. S., Mizukami, H. Oxygen affinity of hemoglobin in persons with acute myocardial infarction and in smokers. Circulation 34: 331–336, August 1966.

(53) Gutenkauf, J. J., Bratt, G. T., Eliot, R. S. Effect of cigarette smoking on the hemoglobin-oxygen dissociation curve. Circulation (Supplement III) 36(4): 129, October 1967.

(9) Birnstingl, M., Cole, P., Hawkins, L. Variations in oxyhaemoglobin dissociation with age, smoking and Buerger's Disease. British Journal of Surgery 54(7): 615–619, July 1967.

(88) Keyes, M. Mizukami, H. Lumry, R. Equilibrium measurement in the reactions of heme-proteins with gaseous ligands. Analytical Biochemistry 18: 126–142, 1967.

(126) Rossi-Fanelli, A., Antonini, E. Studies on the oxygen and carbon monoxide equilibria of human myoglobin. Archives of Biochemistry and Biophysics 77: 478–492, 1958.

(159) Wittenberg, J. B. The molecular mechanism of hemoglobin-facilitated oxygen diffusion. Journal of Biological Chemistry 241(1): 104–114, January 10, 1966.

Anomalous hemoglobin-oxygen dissociation. The 1968 document has misquoted (9) Birnstingl et al. The authors explain the increased hemoglobin affinity for oxygen in smokers as almost entirely due to carbon monoxide. Portions of the Discussion and Summary are as follows:

> **The Effect of Smoking.**—The increase in oxygen affinity found in smokers appeared mainly due to high concentrations of carbon monoxide in the blood of the smokers (Haldane-Smith effect). When the oxygen saturation values had been corrected for HbCO content, the mean oxygen affinity of the group of smokers was much reduced, but it remained significantly above that of the group of non-smokers. This small residual increase remains unexplained. It is unlikely to be due to methaemoglobin, as this was estimated in a few of the samples and the concentrations were found to be low (less than 2 per cent).

SUMMARY

A study has been made of the effects of age, smoking, and Buerger's disease on oxyhaemoglobin dissociation.

Healthy male subjects over 40 years of age have a blood oxygen affinity which is greater than that of a similar group under this age. This would result in a shift to the left of the oxyhaemoglobin dissociation curve.

Cigarette smokers also have an increased oxygen affinity, but this is almost entirely due to a raised carbon monoxide haemoglobin level.

Glucose Metabolism and Possible Cardiovascular Effects

Epstein (*37*) has reviewed the relationships of hyperglycemia to coronary heart disease. Although he states that there appeared to be no relationship of cigarette smoking to the hyperglycemia that was associated with the prevalence of coronary heart disease in the Tecumseh population, Higgins (*63*) reports that the Tecumseh cigarette smokers, both male and female, had approximately a 10 mg. percent elevation in blood glucose as compared to nonsmokers, although the percentage elevations above the median levels were not statistically significant. Since Epstein (*37*) reported that cigarette smokers in the Tecumseh study population had a higher incidence of coronary heart disease, it would be interesting to see what the interrelationship of the incidence of coronary heart disease is to the cigarette smokers who have elevated blood glucose levels.

Cohen, et al. (*24*) have reported abnormal glucose tolerance in some postinfarction patients, suggesting the possibility that this group has difficulty utilizing glucose. It is known that smoking induces release of catecholamines which can create an increased demand for glucose by the body. Wahlberg (*152*) had noted that in patients with atherosclerotic disease but without clinical diabetes mellitus, the glucose tolerance was pathologic in 46 percent as compared with 10 percent of controls, and normal in 33 percent as compared with 71 percent controls. From this he infers that subclinical diabetes mellitus may predispose to vascular disease in the same way as clinical diabetes mellitus.

Kingsbury, et al. (*89*) studied a small group of male patients with peripheral arteriosclerotic disease to determine the serum glucose, nonesterified fatty acids, and immunoreactive insulin responses to subcutaneous adrenaline and to smoking. Under basal conditions, the fatty acid response was normal. While adrenaline consistently caused a rise in serum glucose, cigarette smoking either had no effect or lowered the fasting concentration. In 5 patients smoking caused an elevation in the immunoreactive insulin which could not be explained by blood sugar changes. The implication is that these patients were hypersecretors of insulin. Unfortunately, detailed smoking histories are not available for these individuals. Szanto (*141*), in a very small study of habitual smokers, noted a "hyperinsulinism" response during oral glucose tolerance testing after smoking two cigarettes. This response was markedly reduced when the test was repeated after a 14-day abstinence from smoking. The view that hyperinsulinemia is associated with atherogenesis has been suggested (*114, 118, 149, 157*) and discussed by Mahler (*102*). If smoking directly or indirectly causes a hyperinsulin response in some individuals, then this may possibly be one mechanism by which cigarette smoking may enhance atherogenesis.

Kershbaum, et al. (*86*) have noted higher plasma 11-hydroxy corticosteriod levels in smokers. Whether the "hyperinsulinism" reported to be present in smokers is related to increased adrenal corticosteriods remains to be determined. Hyperinsulinism could be a response to the frequent catecholamine-induced hyperglycemia caused by cigarette smoking in individuals without significant clinical or subclinical coronary heart disease; but conceivably the hyperinsulinism response might be more pathological in coronary patients. Also, the potassium and other ion changes caused by glucose shifts in response to shifts in insulin levels may predispose to cardiac arrhythmias and sudden death.

(37) Epstein, F. H. Hyperglycemia. A risk factor in coronary heart disease. Circulation 36: 609–619, October 1967.

(63) Higgins, M. W., Kjelsberg, M. Characteristics of smokers and nonsmokers in Tecumseh, Michigan. II. The distribution of selected physical measurement and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86(1): 60–77, January 1967.

(152) Wahlberg, F. The intravenous glucose tolerance test in atherosclerotic disease with special reference to obesity hypertension, diabetic heredity and cholesterol values. Acta Medica Scandinavica 171(1): 1–7, 1962.

(89) Kingsbury, K. J., Jarrett, R. J. Effects of adrenaline and of smoking in patients with peripheral atherosclerotic vascular disease. Lancet 2(7505): 22–23, July 1, 1967.

(141) Szanto, S. Smoking and atherosclerosis. British Medical Journal 3: 17 July 15, 1967.

(114) Nikkila, E. A., Vesenne, M-R., Miettinen, T. A., Pelkonen, R. Plasma-insulin in coronary heart disease: Response to oral and intravenous glucose and to tolbutamide. Lancet 2: 505–511, September 11, 1965.

(118) Peters, N., Hales, C. N. Plasma-insulin concentrations after myocardial infarction. Lancet 1: 1144–1145, May 29, 1965.

(149) Vallance-Owen, J. Comments on Dr. Mahler's "Diabetes and Arterial Lipids". Quarterly Journal of Medicine 34(136): 485, October 1965.

(157) Welborn, T. A., Breckenridge, A., Rubenstein, A. H., Dollery, C. T., Fraser, T. R. Serum-insulin in essential hypertension and in peripheral vascular disease. Lancet 1(7451): 1336–1337, June 18, 1966.

(102) Mahler, R. Diabetes and arterial lipids. Quarterly Journal of Medicine 34(136): 484, 1965.

Hyperinsulinism. This page devoted to glucose concludes with the thesis that hyperinsulinism is a link between smoking and atherosclerosis. All the references do not relate to smoking except (141) Szanto, who has published two letters in the British Medical Journal (16 April 1966 and 15 July 1967). The work cited in the second letter has not appeared in a regular article.

Smoking and Atherosclerosis

SIR,—In a previous letter on this subject (16 April 1966, p. 984) I suggested that smoking and dietary sugar affect the arteries in a similar way. Further work with the help of heavy-smoker volunteers indicates that the atherogenic effect of smoking might lie in its ability to induce hyperinsulinism. This conclusion is based on the following experiment.

Twelve male and seven female volunteers were chosen with the only criterion in their selection that they habitually smoked 20 cigarettes, or more, per day. Their ages ranged from 25 to 57 years. After explaining the purpose of the trial, the subjects were asked to fast overnight and abstain from smoking until a fasting blood sample was taken. Each subject then smoked two cigarettes in succession while talking to each other or reading magazines. A second specimen of blood was then withdrawn. After that, each subject was given 100 g. glucose in water, and further specimens of blood were collected at set intervals for blood glucose and serum insulin estimations. According to the original plan, subjects volunteered to abstain from smoking for 14 days after the first part of the experiment, but only three males and two females were able to do so. The above test was then repeated on these subjects. Glucose levels were estimated by the method of Folin and Wu, and serum insulin by immunoassay.

In the accompanying Table are shown the blood glucose and serum insulin levels in the fasting state, before and after smoking two cigarettes, and during the glucose tolerance test. The values found during the period of heavy smoking and after the cessation of smoking for 14 days may also be compared.

If excessive insulin response can be defined as insulin levels rising above 100 microunits per ml. serum during an oral glucose tolerance test[1] then subject No. 4 may not be considered to have hyperinsulinaemia. However, the marked drop in insulin response after she stopped smoking for 14 days indicates a relative hyperinsulinism during the period of heavy smoking. The view that hyperinsulinaemia is atherogenic is well documented.[2-5] The suggestion that it is the factor responsible for the liability of heavy smokers to develop atherosclerosis is an expansion of this theory.—I am, etc.,

Comparison of Blood Glucose and Serum Insulin Levels

Subject and Sex	Stage of Trial	Glucose (mg./100 ml. Blood)					Insulin (μu./ml. Serum)				
		Fasting		30 min.	60 min.	120 min.	Fasting		30 min.	60 min.	120 min.
		Before Smoking	After 2 Cigarettes				Before Smoking	After 2 Cigarettes			
1 M	30 cigarettes day ..	92	100	151	112	90	87	96	150	156	102
	Stopped 14 days ..	73	78	136	105	70	29	32	54	67	47
2 M	30–40 cigarettes day	85	90	127	103	84	52	58	112	109	61
	Stopped 14 days ..	66	83	112	100	80	35	43	63	57	35
3 F	25–30 cigarettes day	93	95	134	119	85	99	93	145	158	94
	Stopped 14 days ..	54	81	126	102	80	86	84	112	110	61
4 F	20–30 cigarettes day	90	95	145	120	87	33	30	95	84	60
	Stopped 14 days ..	73	108	141	114	80	8	11	26	22	13
5 M	50 cigarettes day ..	78	84	135	100	89	53	50	149	124	83
	Stopped 14 days ..	69	87	137	99	90	30	34	66	72	64

STEPHEN SZANTO.

Department of Nutrition,
Queen Elizabeth College,
London W.8.

References

1. Grodsky, G. M., Karam, J. H., Pavlatos, P. C., and Bonham, P. H., *Lancet*, 1965, 1, 790.
2. Nestel, P. A., Mattingley, T. A., Vincenzo, M. S., and Peterson, R., *ibid.* 1964, 2, 414.
3. Peters, N., and Hayes, C. N., *ibid.* 1964, 1, 1111.
4. Vallance-Owen, J., *Lancet*, 1965, 2, 1314.
5. Wickham, T. A., Breckenridge, A., Robinette, A. H., Talley, C. T., and Fraser, T. R., *Lancet*, 1966, 1, 1114.

Smoking and Atherosclerosis

SIR,—Your leader (26 March, p. 755) is a fair comment on the present uncertainty with regard to the effects of smoking on the coronary arteries. "On balance," you state, "the evidence is in favour of smoking being a cause, but it is still incomplete, and it would be greatly strengthened if the physiological and biochemical effects of smoking could be shown to contribute to the development of some parts of the disease process."

In a paper published earlier this year[1] it was shown how heavy smokers depend, in certain cases, on their nicotine consumption to maintain their blood sugar level within normal limits. When these people attempted to break with the habit they developed hypoglycaemic symptoms, and to counteract this they ate sweets in a quantity that was surprising even to themselves.

Recently it has been reported by several workers that refined carbohydrates increase the tendency of the blood platelets to stick to the arterial walls. If nicotine is interchangeable with the refined carbohydrates in maintaining the blood sugar on comfortable levels, is it not plausible that it can also cause an increased platelet stickiness in a similar way? To give this hypothesis a biochemical backing, it is known that nicotine exerts an antidiuretic effect due to its action on the hypothalamus. In a present, as yet unpublished, series of tests it was found that the excessive ingestion of glucose or sucrose by carbohydrate-deprived subjects may inhibit for more than four hours the diuresis that is normally expected following the drinking of a litre of water.—I am, etc.,

STEPHEN SZANTO.

Hertford County Hospital,
Hertford.

Reference

1. Szanto, S., *J. Irish med. Assoc.*, 1966, 243, 22.

Additional Considerations Regarding Coronary Blood Flow

Coronary blood flow, besides being influenced by the size of the inner lumen of the coronary vessel wall and its ability to dilate for the purpose of increasing flow of oxygenated blood when needed by heart muscle, is also dependent upon the viscosity of the blood (*16*). The concepts of fluid mechanics, such as laminar or turbulent flow, are well known. For any given aperture and pumping pressure, fluid flow will depend somewhat upon the physical characteristics of the fluid itself. It has been demonstrated in both cigarette smokers (*199*) and in patients with myocardial infarction that hemoconcentration occurs (*15, 137*), sometimes to a relatively small degree in terms of absolute changes in hematocrit, but the changes in viscosity are much greater than might have been predicted from consideration of hematocrit changes alone. At this point, other factors related to fluid mechanics also enter in, such as the quality and amount of lipids in the blood. Burch, et al. (*15*) have demonstrated that increased fatty acids increase the force necessary to "shear" the blood, thus contributing to a reduction in the capacity of the blood to flow in laminar fashion through a given aperture. When coronary arteries are impaired by partial obstruction of the inner lumen or by decreased distensibility, there may be a critical interaction with blood viscosity causing marked turbulence of flow and thus reducing further the potential for increasing coronary blood flow.

SUMMARY, CONCEPT AND CONCLUSION

Additional evidence has been presented which tends to confirm and extend the positive findings previously reported in the 1964 and 1967 reports.

1. Epidemiological studies show that "heavy" cigarette smoking is strongly associated with an increased risk of dying from coronary heart disease.

2. New data confirm and help to clarify the relationship between cigarette smoking and other "risk factors" in the development of coronary heart disease suggesting that both independent and interacting effects are involved.

3. Evidence indicates that cigarette smoking may accelerate the pathophysiological changes of pre-existent coronary heart disease and contribute to sudden cardiovascular death. This relationship helps to explain why stronger epidemiological correlations between cigarette smoking and coronary heart disease tend to be found in incidence studies rather than in prevalence studies where the population is under-represented for those people who have had fatal outcomes from coronary heart disease.

4. Present evidence continues to support the position that giving up cigarette smoking is beneficial to cardiovascular health.

5. Some progress is being made in the study of the interrelationships of selected psychological factors, smoking behavior, and the development of coronary heart disease.

Recent data provide a basis for the formulation of a theoretical concept by means of which it is possible to correlate the interaction of several known coronary heart disease risk factors with the physiological mechanisms by which cigarette smoking may affect the myocardium.

The epidemiological studies continue to indicate that "heavy" cigarette smoking is strongly associated with a fatal outcome from coronary heart disease. This fact may be accounted for by a mechanism whereby, in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may "trigger" myocardial oxygen deficits of critical degree. One or more of the following mechanisms may be involved in this process:

1. The increase of myocardial wall tension and velocity of contraction, largely mediated through norepinephrine released in response to cigarette smoking, thereby increasing the myocardial demand for oxygen and other nutrients.

2. The relative reduction of nutrient capillary blood flow in the region of the myocardium distal to and dependent upon blood flow through a partially occluded coronary artery.

3. The impairment of oxygen dissociation from hemoglobin due to the formation of carboxyhemoglobin from carbon monoxide, thereby diminishing the availability of oxygen to the myocardium.

4. The reduction of the supply of oxygen available to the myocardium as a consequence of hypoxemia due to severely impaired pulmonary function from chronic obstructive bronchitis.

(106) McDonough, J. R., Hames, G. G., Garrison, G. E., Stulb, S. C., Lehtman, M. A., Hetherington, D. C. The relationship of hematocrit to cardiovascular states of health in the Negro and white population of Evans County, Georgia. Journal of Chronic Diseases 18(3): 243-257, March 1965.

(15) Burch, G. E., DePasquale, N. P. The hematocrit in patients with myocardial infarction. Journal of the American Medical Association 180(1): 63-70, April 7, 1962.

(137) Stables, D. P., Rubenstein, A. H., Metz, J., Levin, N. W. The possible role of hemoconcentration in the etiology of myocardial infarction. American Heart Journal 73(2): 155-160, February 1967.

5. The impairment of coronary blood flow as a result of the increased blood viscosity associated with hyperlipemia or hemoconcentration.

6. The increase in platelet adhesiveness which might contribute to thrombus formation or coronary occlusion.

7. The predisposition to acute cardiac arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release.

8. The possible, although presently speculative, contributions to impairment of myocardial cellular respiration by cyanide ion.

Thus, the interaction of the factors which decrease oxygen supply to the myocardium and those which increase the myocardial demand for oxygen may play a major role in precipitating the fatal outcome in some individuals with coronary heart disease. On the other hand, it is possible that the same factors, in less severe clinical circumstances, could precipitate temporary coronary insufficiency or contribute to nonfatal myocardial infarctions or cardiac arrhythmias.

The pathophysiological factors associated with cigarette smoking may further interact with other known epidemiological risk factors associated with coronary heart disease such as high serum cholesterol and high blood pressure. Although not a "risk factor", unusually high physical stress may also create physiological demands for additional oxygen supply to the myocardium.

The finding that those who discontinue cigarette smoking have a lower risk of dying from coronary heart disease than those who continue to smoke might be accounted for by the potential reversibility of many of the pathophysiological effects of smoking on the cardiovascular system. It is reasonable to expect partial reversibility of factors that interfere with oxygen supply, such as the carbon monoxide effect, and the increased platelet adhesiveness, hyperlipemia, and hemoconcentration noted in cigarette smokers. Moreover, the increased myocardial oxygen requirements associated with the cigarette smoking-induced catecholamine response and neurogenic reflexes could be expected to be eliminated upon cessation of cigarette smoking. In some patients, the cardiopulmonary benefits of stopping smoking may reduce pulmonary hypertension.

An increased ability to predict future cardiovascular events in individual persons will depend upon more precise definition and measurement of the pathophysiologic factors associated with cigarette smoking and their correlation with information about the epidemiological risk factors.

Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

"Trigger" Mechanisms for Cigarette Smoking. The impressive list of 8 mechanisms is not supported by sections in the 1968 document. It should be noted once more that for each mechanism, cigarette smoking was not used as the stimulus. In most instances, catecholamines, carbon monoxide and large doses of nicotine were used to elicit the "trigger" menchanism. The brief comments for each of the 8 in the list are as follows:

1. Increase in myocardial wall tension was elicited by doses of nicotine and cigarette smoke large enough to cause a rise in blood pressure in anesthetized dogs.
2. There are no observations that nicotine or catecholamines can reduce collateral blood flow.
3. The amount of carboxyhemoglobin in an ordinary smoker is about 5%.
4. Smokers have no impairment in pulmonary function unless they are suffering from chronic lung disease.
5. The lipidemia and hemoconcentration demonstrated acutely following smoking is not intense enough to impair blood flow.
6. The increase in platelet adhesiveness is not consistently found in most smokers. Furthermore, thrombosis has not been noted in animals receiving toxic doses of nicotine for an extended period of time.
7. The predisposition to acute cardiac arrhythmias was observed only in dogs exposed to huge quantities of cigarette smoke for 30 minutes.
8. The role of cyanide in cigarette smoking has not been proven.

SMOKING AND CEREBROVASCULAR DISEASES

Many of the pathophysiological considerations noted in the above section may also pertain to the relationship of smoking and cerebrovascular disease.

A mortality study in Japan by Hirayama (*65*) reports findings different from those cited in the 1967 Report (*146*), in which smokers under age 75 had a mortality ratio of 1.40, or more, for stroke.

Hirayama found that deaths due to vascular lesions of the central nervous system, after age 40, were one-third less frequent among smokers than among nonsmokers. Several factors may account for these different findings. One is that the etiologic spectrum for stroke in Japan includes more hemorrhagic strokes than in the United States. Another is that the Japanese study included all stroke deaths over age 40, whereas the studies in the United States found the positive association between smoking and stroke mortality occurred under age 75 (*54*).

In a study reported by Kuhn (*93*), 20 habitual smokers refrained from smoking for one-half day and baseline retrograde brachiocerebral angiograms were taken; then they smoked one cigarette, inhaled deeply, and had repeat angiograms. Only those over 60 years of age failed to have significant acceleration of flow in cerebral precapillary vessels and markedly increased vessel counts as in carbon dioxide inhalation experiments.

As in coronary heart disease, it may be that smoking has different effects depending upon the degree of underlying arteriosclerotic disease present. Among patients with stroke, many have arteriosclerotic heart disease and a significant number die of myocardial infarcts (*104*).

The rate of oxygen uptake in the brain is very high, being approximately 5 cc. oxygen/100 g. brain/min. (*104*). As discussed in the cardiovascular section, if carbon monoxide causes a shift to the left in the oxygen hemoglobin dissociation curve, it would make less oxygen available to the brain tissue. Those people with an arteriosclerotic cerebrovasculature who cannot increase their cerebral blood flow in response to smoking may therefore more easily develop a state of relative cerebral hypoxia; a situation which could be a factor in the etiology of stroke.

(93) KUHN, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. Annals of the New York Academy of Sciences 142 (Article 1): 67–71, March 15, 1967.

(104) MEYER, J. S. Personal communication. 1968.

The Health Consequences of SMOKING

1969 SUPPLEMENT TO THE

1967 Public Health Service Review

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

CHAPTER 1

Smoking and Cardiovascular Diseases

Contents

Summary

Coronary heart disease (CHD) among men in the Western world is an epidemic which cuts short the lives of many in their prime productive years. The evidence linking smoking and CHD has been reported not only from studies in the United States, but also from such diverse areas as West Germany, the U.S.S.R., France, Israel, Italy, and the British Isles.

The 1968 Supplement (27) stated:

> Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can contribute to the development of cardiovascular disease and particularly to death from coronary heart disease.

The convergence of autopsy data and experimental data presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis, including that of the coronary arteries. The results of physiological research and the findings of diminished risk of CHD in those who have stopped smoking indicate that there is also a more immediate mechanism operative. The mechanisms which might be responsible for the promotion of myocardial infarction and fatal cardiac arrhythmias by cigarette smoking were extensively reviewed in the 1968 Supplement (27). Briefly stated, nutrient supply to the myocardium in general and, perhaps more importantly, to focal ischemic areas of the myocardium may be seriously compromised by a combination of effects caused by smoking, and the deprived myocardium may become infarcted or develop an arrhythmia. These effects include diminution of blood flow through atherosclerotic coronary vessels and diminution of available oxygen for tissue use resulting from the binding of carbon monoxide to hemoglobin in the place of oxygen and possibly, although presently speculative, the poisoning of respiratory enzymes by hydrogen cyanide.

Cigarette smoking has been shown to be an important risk factor in the development of CHD. It is important both by itself and in the presence of other significant risk factors. In combination with certain other risk factors, the joint effects appear to be even greater than those accounted for by those risk factors independently.

Epidemiological Studies

Hammond, et al. (11) have presented new data on mortality from CHD, stroke, and nonsyphilitic aortic aneurysm among more than 800,000 men and women who were between the ages of 40 and 79 in 1959. The authors were attempting to evaluate the significance of multiple factors (sex, age, diabetes, high blood pressure, body weight, change in weight, exercise, cigarette smoking, sleep, and nervous tension) in the variations in death rates from these three diseases. It should be noted that this information consisted of self-reports obtained by questionnaire and were not obtained from medical examination. Causes of death were based on death certificate reports.

As illustrated in table 1, coronary heart disease death rates and mortality ratios increased with increased cigarette smoking for men in all age groups and for women under the age of 70. Although the mortality ratios were higher in the younger age groups, the differences in death rates between nonsmokers and heavy smokers became progressively higher with increasing age. Although CHD rates were highest for those who were 10 percent or more above the average weight for their height-age-sex group, and for those who reported having high blood pressure, the trend is clear that the effect of smoking persists and is appreciable, even when these other factors are held constant (table 2).

(27) U.S. Public Health Service. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696. 1968. 117 pp.

(11) Hammond, E. C., Garfinkel, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Archives of Environmental Health 19(2): 167-182, August 1969.

TABLE 1.—*Death rates and mortality ratios for coronary heart disease and stroke, by amount of cigarette smoking, sex, and age*

Sex and age	Coronary heart disease					Stroke				
	Never smoked cigarettes regularly	Regularly smoked cigarettes				Never smoked cigarettes regularly	Regularly smoked cigarettes			
		Number smoked daily					Number smoked daily			
		1-9	10-19	20-39	40 or more		1-9	10-19	20-39	40 or more
DEATH RATES										
Males:										
40-49 years	68	100	176	226	375	14	30	[8]16	31	33
50-59 years	257	409	544	616	715	40	78	80	81	96
60-69 years	650	961	1,194	1,241	1,404	168	219	242	272	253
70-79 years	1,730	1,970	2,431	2,573	2,543	650	817	808	792	[8]445
Females:										
40-49 years	13	17	27	47	[8]43	10	15	26	29	[8]87
50-59 years	50	68	140	153	220	27	34	73	72	[8]95
60-69 years	258	279	479	558	[8]542	110	139	235	201	—
70-79 years	979	740	963	1,283	—	457	404	[8]276	622	—
MORTALITY RATIOS[1]										
Males:										
40-49 years	1.00	1.69	2.99	3.76	6.31	1.00	2.79	[8]1.16	2.21	1.64
50-59 years	1.00	1.59	2.13	2.40	2.79	1.00	1.95	1.45	2.03	2.40
60-69 years	1.00	1.45	1.82	1.91	1.79	1.00	1.30	1.44	1.62	1.72
70-79 years	1.00	1.14	1.41	1.49	1.47	1.00	.85	.92	1.22	[8].68
Females:										
40-49 years	1.00	1.31	2.08	3.62	[8]3.31	1.00	1.50	2.60	2.90	[8]8.70
50-59 years	1.00	1.13	2.37	2.64	3.73	1.00	1.26	2.70	2.67	[8]3.52
60-69 years	1.00	1.04	1.73	2.08	[8]2.02	1.00	1.26	2.15	1.83	----
70-79 years	1.00	.76	.98	1.27	----	1.00	.83	[8].57	1.28	----

[1] The mortality ratio is the observed rate divided by the expected rate.
[8] Rates based upon only 5 to 9 deaths.

SOURCE: Hammond, E. C., et al. (11).

TABLE 2.—*Coronary heart disease death rates for men and women classified by smoking habits, age, blood pressure, and relative weight*

Extent of cigarette smoking and age	No high blood pressure, by relative weight					High blood pressure, by relative weight				
	Total	Less than 90	90-109	110-119	120 and over	Total	Less than 90	90-109	110-119	120 and over
MEN										
None or slight:										
40-49 years	52	[8]27	45	64	128	204	---	195	[8]210	-----
50-59 years	226	140	218	253	370	630	[8]656	611	643	609
60-69 years	603	542	573	701	763	1,503	1,777	1,293	1,560	1,555
70-79 years	1,611	1,467	1,555	1,840	1,858	2,733	3,342	2,568	2,651	3,100
Intermediate:										
40-49 years	118	106	104	141	245	349	[8]354	266	[8]286	-----
50-59 years	373	352	363	435	538	876	1,424	636	1,182	995
60-69 years	958	814	870	944	973	1,876	1,913	1,999	1,447	1,710
70-79 years	1,973	2,237	1,776	1,953	2,901	3,230	3,700	3,172	2,213	6,451
20 or more:										6
40-49 years	222	123	235	309	278	647	897	550	765	88[8]
50-59 years	530	422	536	666	641	1,137	1,143	1,153	923	1,41
60-69 years	1,047	978	1,019	1,249	1,307	1,915	2,150	1,913	1,744	2,075
70-79 years	2,286	2,346	2,205	2,151	2,846	4,123	5,141	4,205	[8]3,672	-----
WOMEN										
None or slight:										
40-49 years	8	[8]6	7	---	22	63	---	83	-----	76
50-59 years	41	39	32	64	68	161	100	162	157	229
60-69 years	201	153	191	265	323	469	400	475	462	459
70-79 years	776	832	779	657	756	1,338	1,313	1,217	1,449	1,626
Intermediate:										
40-49 years	15	17	12	---	---	86	---	[8]76	-----	-----
50-59 years	76	69	70	153	[8]73	281	361	281	[8]253	[8]198
60-69 years	294	337	346	423	---	730	723	743	848	[8]454
70-79 years	607	736	651	---	---	1,161	[8]1,854	1,014	-----	-----
20 or more:										
40-49 years	36	25	33	[8]42	[8]72	144	---	198	-----	-----
50-59 years	120	118	128	---	[8]135	358	[8]293	291	[8]664	[8]706
60-69 years	467	341	522	[8]637	---	911	[8]795	1,100	-----	-----
70-79 years	644	[8]866	[8]565	---	---	2,453	---	[8]3,743	-----	-----

[8] Rates based upon only 5 to 9 deaths.

SOURCE: Hammond, E. C., et al. (11).

Hammond, et al. also studied CHD mortality among men who were ex-smokers of cigarettes. The death rates from CHD were lower among the ex-smokers than among those still smoking at the beginning of the study, the size of the difference being larger the longer they had been off smoking (table 3). Some people stop smoking because of illness or symptoms and these people would be expected to have higher death rates than those who stop for other reasons. Early deaths among those with preexisting disease may account, at least in part, for the high death rates from CHD among ex-smokers in the early years of abstention.

Mortality ratios for stroke were higher among cigarette smokers with the exception of those over 70 years of age. Male ex-cigarette smokers had mortality ratios for stroke approximately equal to those of nonsmokers.

A clear increase in mortality from nonsyphilitic aortic aneurysms with increasing cigarette smoking among men aged 50–69 is seen in table 4. The mortality ratio for heavy smokers was 8.00.

Hammond, et al. found that death rates from the three diseases varied considerably with relative weight, amount of exercise, amount of cigarette smoking, and hours of sleep per night. Subjects who were obese, took little or no exercise, smoked many cigarettes a day, or slept 9 or more hours per night had high death rates. Those with a combination of these factors have especially high death rates from the three diseases.

TABLE 3.—*Observed and expected number of deaths and mortality ratios for ex-cigarette smokers with a history of smoking only cigarettes, by number of years since last cigarette smoking and for current cigarette smokers, coronary heart disease and stroke; compared to persons who never smoked regularly, in men aged 40–79*

Type of smoker	Coronary heart disease			Stroke		
	Observed	Expected	Ratio	Observed	Expected	Ratio
Ex-cigarette smokers (former smokers of 1–19 cigarettes a day):						
Stopped:						
Less than 1 year	29	17.9	1.62	———	———	———
1–4 years	57	46.6	1.22	———	———	———
5–9 years	35	63.7	1.55	———	———	———
10–19 years	52	54.1	.96	———	———	———
20 or more years	70	64.7	1.08	———	———	———
Total	303	226.9	1.16	57	56.9	1.00
Current cigarette smokers	1,023	551.5	1.93	207	134.5	1.54
Never smoked regularly	1,841	1,841.0	1.00	301	301.0	1.00
Ex-cigarette smokers (former smokers of 20 or more cigarettes a day):						
Stopped:						
Less than 1 year	62	38.6	1.61	———	———	———
1–4 years	154	271.9	1.41	———	———	———
5–9 years	155	114.3	1.16	———	———	———
10–19 years	125	136.1	1.23	———	———	———
20 or more years	80	78.4	1.65	———	———	———
Total	384	427.7	1.28	96	101.1	0.93
Current cigarette smokers	2,872	1,104.7	2.33	446	234.7	1.87
Never smoked regularly	1,841	1,841.0	1.00	301	301.0	1.00

* Source: Hammond, E. C., et al. (11).

15

TABLE 4.—*Aortic aneurysm death rates and mortality ratios for men aged 50–69, classified by cigarette smoking habits*

[Rates per 1,000 population]

Measure	Never smoked regularly	Current smokers, by daily cigarette consumption			
		1–9	10–19	20–39	40 or more
Death rate	13	34	50	59	104
Mortality ratio	1.00	2.62	3.85	4.54	8.00

Source: Hammond, E. C., et al. (11).

They also found that death rates from CHD and stroke were lower in ex-cigarette smokers than in men who were currently smoking cigarettes at the time they enrolled in the study. The death rates of male ex-cigarette smokers who had not smoked for 10 to 20 years were no higher or only slightly higher than the death rates of men who had never smoked regularly. Death rates from the three diseases were lowest among subjects without a history of diabetes or high blood pressure who were not obese, took at least moderate exercise, never smoked regularly and slept 6 to 8 hours per night. Nevertheless, even these subjects had substantial death rates from CHD, stroke and nonsyphilitic aortic aneurysms.

Stamler (24) has analyzed 10-year mortality data on a total cohort of men, aged 40–59 in 1958, who were employees of the Chicago Peoples Gas Light and Coke Co. Of 1,465 men examined, 1325 were found initially to be free of definite CHD and have been followed without systematic intervention. Higher overall death rates were found among the smokers in the study. Table 5 shows the death rates from CHD and from all causes for men with various risk factors.

Recent papers by Thorne, et al. (25) and by Paffenbarger, et al. (19) report further results of studies of CHD among former college students. College health records and other college records were reviewed to ascertain the presence or absence of factors under consideration. Cases were identified from death certificates in the study of fatal CHD (19) and from questionnaires and physical examinations in the study of nonfatal CHD (25). Matched controls were obtained for each case. In both nonfatal and fatal CHD, significantly more smokers were found among the cases than among the controls. Combinations of risk factors resulted in greater CHD morbidity and mortality ratios than did single factors. Figure 1 shows the morbidity ratios for combinations of pairs of risk factors in nonfatal CHD and table 6 shows mortality ratios for combinations of risk factors in fatal CHD.

(24) Stamler, J. Personal Communication. 1969.

(25) Thorne, M. C., Wing, A. L., Paffenbarger, R. S., Jr. Chronic illness in former college students. VII. Early precursors of nonfatal coronary disease. American Journal of Epidemiology 87(3): 509–523. May 1.

(19) Paffenbarger, R. S., Jr., Wing, A. L. Characteristics in college years disposing to fatal coronary heart disease in later life. (In press) American Journal of Epidemiology: 1969.

TABLE 5.—*10-year mortality rates for sudden death, coronary heart disease, stroke, cardiovascular-renal, and all causes combined among men aged 40–59, classified according to cigarette smoking, cholesterol, and blood pressure*

[Peoples Gas Light Co. study, 1956–65. Men originally free of coronary heart disease and followed without systematic intervention.]

1958 risk factor status—cigarette smoking (10 or more a day), hypercholesterolemia, hypertension [1]	10-year mortality											
	Sudden death			All CHD		Stroke		All CVR		All causes		
	Number of men in cohort	Number of deaths	Death rate [2]	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate	Number of deaths	Death rate
No risk factor	254	0	0	1	3.6	2	8.0	4	15.9	23	92.6
Hypercholesterolemia or hypertension only—1 factor	216	4	18.4	15	69.1	4	18.6	19	72.6	27	124.8
Cigarette smoking only (10 or more a day)—1 factor	495	6	12.0	15	27.1	5	11.0	20	44.9	44	107.7
Hypercholesterolemia and hypertension only—2 factors	60	1	8.9	3	26.6	1	10.7	4	38.3	6	121.9
Cigarette smoking (10 or more a day) and hypercholesterolemia or cigarette smoking and hypertension—2 factors	288	11	32.2	17	57.1	6	19.9	26	86.4	33	168.8
Cigarette smoking (10 or more a day), hypercholesterolemia, hypertension—all 3	67	2	25.1	6	70.0	2	25.4	6	101.6	17	223.8
Total	[3] 1,373	23	16.9	61	38.2	22	14.0	81	56.0	162	113.1

[1] Risk factors include: Serum cholesterol 250 or more mg. ml.; diastolic blood pressure 90 or more mm. Hg; 10 or more cigarettes/day.

[2] All rates are age-adjusted by 6-year age groups to the U.S. male population, 1960. All rates per thousand.

[3] Smoking data were not obtained for 4 of the 1,325 men.

Source: Stamler, J. (24).

TABLE 6.—*Estimated coronary heart disease death ratios in a 17–51 year follow-up among former college students, classified according to combined presence (+) or absence (−) of each of three specified risk factors, and by age*

Risk factor			Age (years) at death from coronary heart disease			
Cigarettes, 1 or more per day	Systolic B.P. 150 or more mm. Hg	Ponderal index, less than 13.5	Total 40–59 years	40–44 years	45–51 years	52–59 years
+	+	+	4.3	[1] (1.9)	3.7	[1] (4.5)
+	−	+	1.8	2.3	1.6	[1] (2.0)
+	+	−	4.2	2.9	4.5	5.6
−	+	+	1.9	2.9	1.6	1.3
+	−	−	1.7	2.2	1.9	1.3
−	+	−	1.3	1.2	1.2	1.4
−	−	+	1.1	1.4	1.4	.8
−	−	−	1.0	1.0	1.0	1.0

[1] Numbers in parentheses indicate expected number coronary heart disease deaths less than 5.

Source: Paffenbarger, R. S., et al. (19).

In a study of participants in the Health Insurance Plan of New York, Weinblatt, et al. (29) reported that cigarette smoking males who developed angina pectoris were more likely to develop infarction than were nonsmoking anginal patients, but there were not enough cases to draw definite conclusions.

Weinblatt, et al. (30) also reported that the prognosis after the development of a myocardial infarction appears to be independent of smoking status prior to the infarct. In the absence of data indicating which patients stop smoking and how stopping smoking is related to the severity of myocardial damage, one cannot evaluate the effect of smoking on prognosis. If the persons who stop smoking tend to include the most debilitated, the effect of continued smoking on prognosis would be underestimated.

In a prospective study of over 3,000 men, Jenkins, et al. (14) reported that the incidence of CHD in men aged 39–49 was three times higher among the cigarette smokers than among the nonsmokers (table 7). The incidence of CHD increased with increased daily cigarette consumption. For men aged 50–59, the relationship between cigarette smoking and CHD was found to be significant only for the heavy

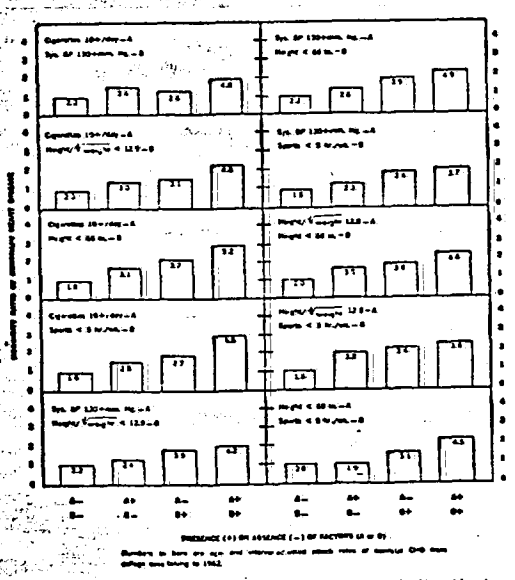


FIGURE 1.—Morbidity ratios of coronary heart disease for paired combinations of factors in college.

SOURCE: Thorne, M.C., et al. (25).

smokers (table 8). Former cigarette smokers also had significantly higher CHD incidence rates, but no data are given on length of time since stopping smoking, or reasons for stopping. Pipe and cigar smokers did not have higher CHD incidence rates. After controlling for other risk factors such as lipid levels, diastolic blood pressure, and body build, the authors found that the association between cigarette smoking and CHD remained (tables 9, 10). The relationship between smoking and CHD was stronger among those men who exhibited behavior type A than those exhibiting behavior type B (tables 11, 12). Behavior type A is characterized by enhanced competitiveness, drive, aggressiveness, hostility, and an excessive sense of time urgency. Behavior type B indicates an absence of these characteristics. Analysis of the data on behavior and cigarette smoking showed that both factors have effects on the CHD rate. Again, these associations were stronger in the younger age group.

(29) WEINBLATT, E., FRANK, C. W., SHAPIRO, S., SAGER, R. V. Prognostic factors in angina pectoris—a prospective study. Journal of Chronic Diseases 21(4): 231–245, July 1968.

(30) WEINBLATT, E., SHAPIRO, S., FRANK, C. W., SAGER, R. V. Prognosis of men after first myocardial infarction: Mortality and first recurrence in relation to selected parameters. American Journal of Public Health and the Nation's Health 58(8): 1329–1347, August 1968.

(14) JENKINS, C. D., ROSENMAN, R. H., ZYZANSKI, S. J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1140–1147, December 1968.

Prognosis of Myocardial Infarction. The article by (30) Weinblatt et al. is being criticized for absence of data indicating which patients stop smoking. The article did not mention exsmokers. Only smokers and nonsmokers are reported. Anyway, the basis for statement that prognosis is independent of smoking states is as follows:

Table 4—Early mortality among men following first MI in relation to physical activity level and smoking habits at time of MI, age-adjusted per cent dead within one month

Characteristic at time of MI	No.	% dead (age-adj.)
Physical activity level*		
Least active	261	43.6
Other classified	523	25.0
Intermediate	280	28.6
Most active	243	20.5
Least active, no limitation of activity prior to MI	200	40.4
Men without prior CHD		
Least active	186	38.8
Other classified	426	22.6
Men without elevated blood pressure		
Least active	143	36.1
Other classified	365	19.5
Men with neither prior CHD nor elevated blood pressure		
Least active	108	30.0
Other classified	299	17.6
Men without other CV disease		
Least active	211	37.4
Other classified	466	22.7
Smoking habits		
All cigarette smokers†	487	32.6
Two or more packs daily	177	27.1
Less than two packs daily	304	35.2
Pipe and/or cigar smokers	110	27.5
Nonsmokers	237	38.0

*Description of the construction of the physical activity classes used in the HIP study has been published (J. Chron. Dis. 18:527, 1965). In general, the three levels are defined in terms of specified combinations of four classes of job-connected activity and four classes of off-job activity. Each of the job-connected and off-job categories is defined as a specified range of accumulated scores of the weights assigned to specific questionnaire items.

†Includes six cigarette smokers, amount unknown.

Cigarette smoking—especially heavy cigarette smoking—has been reported as associated with an increased risk for incidence of first MI among men in the HIP study population,[6] but no influence of smoking on early mortality could be demonstrated from the preliminary data.[2] This finding is confirmed by the data shown for the full cohort in Table 4.

TABLE 7.—*Annual incidence rates of coronary heart disease for men 30–49 years of age, classified by smoking history and by current practices as to cigarette smoking*

[Age as of the beginning of the 4½ year period of observation]

Morbidity status	Total subjects		Smoking history								Current cigarette smoking by number per day							
			Never smoked		Pipe and cigar only		Former cigarette		Current cigarette		None		1–15		16–25		26 or more	
	Number	Rate[1]	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total number at risk	2,873	.....	340	.....	465	.....	229	.....	1,004	.....	1,121	.....	211	.....	434	.....	422	.....
Total number CHD cases	83	8.2	7	[2] 2.9	3	1.6	10	[2] 9.3	63	[2] 16.9	20	[2] 3.7	5	4.3	13	[2] 8.3	20	[2] 10.6
All myocardial infarction	62	6.1	4	1.7	3	1.6	10	9.3	35	7.3	17	3.1	4	4.2	13	6.7	15	9.3
Symptomatic	34	3.7	1	.4	2	1.1	8	7.4	27	5.6	11	2.0	4	4.2	11	5.6	12	6.3
Unrecognized	16	1.4	3	1.2	1	.5	2	1.9	8	1.7	6	1.1	0	0	2	1.0	6	3.1
Fatal	9	.9	0	0	0	0	1	.9	8	1.7	1	.2	0	0	0	2.6	3	1.6
Angina pectoris only	11	1.1	3	1.2	0	0	0	0	8	1.7	3	.6	1	1.0	0	2.6	2	1.1

[1] Annual rate per 1,000 men at risk.

[2] These distributions of cases for various smoking categories are significantly different from chance at P=0.01.

[3] Difference in CHD frequency between this group and those who never smoked cigarettes (col. 1 and 2 combined) is significant at P=0.01 by chi square test corrected for continuity.

[4] Difference in CHD frequency between this group and current noncigarette smokers is significant at P=0.01.

Source: Jenkin, C. D., et al. (11).

TABLE 8.—*Annual incidence rates of coronary heart disease for men 60–69 years of age, classified by smoking history and by current practices as to cigarette smoking*

[Age as of the beginning of the 4½ year period of observation]

Morbidity status	Total subjects		Smoking history								Current cigarette smoking by number per day							
			Never smoked		Pipe and cigar only		Former cigarette		Current cigarette		None		1–15		16–25		26 or more	
	Number	Rate[1]	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total number at risk	934	.....	132	.....	161	.....	137	.....	444	.....	453	.....	109	.....	167	.....	165	.....
Total number CHD cases	79	16.9	9	[2] 11.0	11	13.2	8	14.6	41	20.6	23	[2] 12.3	6	12.2	16	21.3	[2] 19	21.6
All myocardial infarction	62	12.5	6	7.3	8	11.0	6	8.1	33	16.3	19	8.7	5	10.2	15	20.0	13	17.6
Symptomatic	35	8.4	4	4.9	4	5.5	4	5.5	23	11.6	12	5.5	4	8.2	11	14.6	8	10.8
Unrecognized	17	4.1	2	2.4	4	5.5	1	1.6	10	5.0	7	3.2	1	2.0	4	5.3	5	6.7
Fatal	14	3.4	0	0	3	4.1	3	4.9	8	4.0	6	2.8	2	4.1	4	5.3	2	2.7
Angina pectoris only	18	4.3	3	3.7	3	4.1	4	6.5	8	4.0	10	4.6	1	2.0	1	1.3	6	8.1

[1] Annual rate per 1,000 men at risk.

[2] These distributions of cases for various smoking categories could occur 0.10 of the time by chance, hence are not significant at P=0.05.

[3] Difference in CHD frequency between this group and current noncigarette smokers is significant at P=0.01.

Source: Jenkins, C. D., et al. (11).

TABLE 9.—*Annual incidence rates of new coronary heart disease, by smoking habits, adjusted for age and seriatim, for specified other risk factors*

[Rates are annual incidence per 1,000 men, aged 30 to 49 years at entry into study]

Specified other risk factors	Never smoked	Former cigarette smokers	Pipe and cigar only	Daily cigarette consumption			p.[1]
				1-15	16-25	26 or more	
Cholesterol	33	83	22	49	89	100	0.005
Beta-alpha ratio	31	81	15	49	91	102	.001
Lipalbumin	31	85	16	51	89	102	.002
Systolic BP	31	81	15	49	95	100	.001
Diastolic BP	29	89	16	49	95	104	.001
Ponderal index	29	81	16	49	95	107	.001
Physical activity	29	83	15	47	93	104	.001
Amount of exercise	29	81	15	49	93	104	.001
Income level	29	91	16	49	93	104	.001
All of the above	26	83	20	81	89	86	.007
Triglycerides	31	88	20	40	83	104	.002

[1] Level of significance of F-ratio for analysis of covariance.

Source: Jenkins, C. D., et al. (*14*).

TABLE 10.—*Annual incidence rates of new coronary heart disease, by smoking habits, adjusted for age and seriatim, for specified other risk factors*

[Rates are annual incidence per 1,000 men, aged 50 to 59 years at entry into study]

Specified other risk factors	Never smoked	Former cigarette smokers	Pipe and cigar only	Daily cigarette consumption			p.[1]
				1-15	16-25	26 or more	
Cholesterol	116	142	153	115	211	304	0.154
Beta/alpha ratio	107	142	144	130	213	302	.127
Lipalbumin	109	140	151	122	218	302	.135
Systolic BP	118	127	144	129	211	296	.136
Diastolic BP	109	127	135	127	230	273	.066
Ponderal index	107	131	149	122	222	269	.054
Physical activity	113	142	149	115	213	249	.216
Amount of exercise	113	144	151	113	211	255	.263
Income level	113	138	147	120	220	258	.156
All of the above	113	118	138	140	213	258	.158
Triglycerides	113	147	141	90	195	260	.121

[1] Level of significance of F-ratio for analysis of covariance.

Source: Jenkins, C. D., et al. (*14*).

1005050694

TABLE 11.—*Incidence of new coronary heart disease, by smoking category and behavior type, for men aged 30–49*

[Rates are age-adjusted annual incidence per 1,000 men]

Behavior type	Never smoked		Former cigarette smokers		Current and former pipe and cigar only		Daily cigarette consumption						Total	
							1-15		16-25		26 or more			
	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases
A	6.3	5	13.8	7	1.3	1	1.6	1	16.8	15	16.9	16	9.3	45
B	1.3	2	3.1	3	2.2	2	7.3	4	3.1	3	4.9	4	3.3	18
Total	2.9	7	9.1	10	1.8	3	4.9	5	8.3	18	10.4	20	6.2	63

Source: Jenkins, C. D., et al. (*14*).

TABLE 12.—*Incidence of new coronary heart disease, by smoking category and behavior type, for men aged 50–59*

[Rates are age-adjusted annual incidence per 1,000 men]

Behavior type	Never smoked		Former cigarette smokers		Current and former pipe and cigar only		Daily cigarette consumption						Total	
							1-15		16-25		26 or more			
	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases
A	12.4	6	18.6	8	21.8	8	18.4	8	21.5	9	30.0	14	20.4	48
B	10.0	4	8.1	1	8.4	3	6.7	1	21.1	7	19.1	8	12.0	21
Total	11.1	9	16.2	9	14.9	11	11.6	6	21.3	16	26.0	19	13.8	70

Source: Jenkins, C. D., et al. (*14*).

Epidemiological studies linking smoking and CHD have been carried out in various countries. In a retrospective study in Dublin, of 400 patients under the age of 65 who experienced myocardial infarction, Mulcahy, et al. (18) observed a definite association between smoking and the development of the disease.

A prospective epidemiological study of risk factors of CHD, in an Israeli population, indicates that smoking is associated with a higher risk of CHD (17).

In a retrospective study of 503 male patients with myocardial infarction and 714 age-matched controls in Munich, Schimmler, et al. (22) report that cigarette smoking plays a significant role as a risk factor.

A recent paper by Cederlof, et al. (5) employs the twin-study method on a population of American twins, using a similar approach to that previously employed in a Swedish twin population. The purpose is to compare the contribution of genetic and environmental influences to the development of angina pectoris. The authors imply that their study indicates a more important role for genetic factors than for smoking. However, this study can be criticized on several grounds. The authors based their detection of angina pectoris on the results of a self-administered questionnaire designed to elicit a history of chest pain of presumable cardiac origin; previous studies in Swedish twins have shown a low rate of clinical confirmation of heart disease in those classified positive by questionnaire. No data are available on the health and smoking habits of 38 percent of the original group or the 41 percent of the "eligible twin pairs" who were nonrespondents. The authors' definition of a present smoker includes persons who have stopped smoking cigarettes for up to 3 years and thus includes persons who in other studies have been classified as ex-smokers. This definition of a cigarette smoker might contribute to an underestimation of the immediate effect of current cigarette smoking, since an unstated number of recent ex-smokers are included in the same category as current cigarette smokers.

The relationship between cigarette smoking and the development of angina pectoris has not been clarified. However, Aronow, et al. (1) have shown that smoking one cigarette before exercising reduces the energy expenditure required for patients with classical angina pectoris to develop chest pain while exercising on a bicycle ergometer.

(18) Mulcahy, R., Hickey, N., Maurer, B. Coronary heart disease, a study of risk factors in 400 patients under 60 years. Geriatrics 24(1):106–114, January 1969.

(17) Modan, J. H., Katz, H. A., Groen, J. J. Neufeld, H. N., Rissa, E. The prevalence of ischemic heart disease in relation to selected variables. Israel Journal of Medical Sciences 4(4):750–760, July–August 1968.

(22) Schimmler, W., Nery, C., Schimert, G. Risikofaktoren und Herzinfarkt. Eine retrospektive Studien. Münchener Medizinische Wochenschrift 110(27):1585–1591, July 5, 1968.

(5) Cederlof, R., Friberg, L., Hrubec, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. A study on American twins. Archives of Environmental Health 18(6):931–940, June 1969.

(1) Aronow, W. S., Kaplan, M. A., Jacob, D. Tobacco: A precipitating factor in angina pectoris. Annals of Internal Medicine 69(3):529–536, September 1968.

Atherosclerosis

A review of autopsy studies by Strong and Auerbach, suggesting that cigarette smoking has a chronic effect leading to advanced degrees of atherogenesis, was presented in the Health Consequences of Smoking, 1967 (26). Further studies have recently been published in this area.

Sackett, et al. (21) have demonstrated a clear dose-relationship between cigarette smoking and the severity of aortic atherosclerosis at autopsy. Their study of 1,919 consecutive autopsies, on patients who had been interviewed about their smoking habits prior to death, showed a significant increase in the severity of aortic atherosclerosis with increasing use of cigarettes, measured both by intensity and by duration of smoking.

An autopsy study from Russia by Avtandilov, et al. (3) demonstrated a significantly greater degree of atherosclerosis in the coronary arteries of smokers than in those of nonsmokers.

Viel, et al. (23) have reported on the severity of coronary atherosclerosis at autopsy of 1,150 men and 200 women who died violent deaths in Chile. Information on smoking habits was available on 566 men. The authors report no relationship between atherosclerotic lesions and the use of tobacco. The degree of atherosclerosis was expressed as the percentage of the surface of the intima of the left anterior descending coronary artery covered by fatty streaks and fibrous plaques. An examination of the data presented in graphic form indicates that the moderate and heavy smokers appear to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.

A study by Astrup was reviewed in the 1968 Report (37). This study showed that in rabbits on a high cholesterol diet, chronic carbon monoxide exposure has a marked atherogenic effect.

(26) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

(21) Sackett, D. L., Gibson, R. W., Bross, I. D. J., Pickren, J. W. Relation between aortic atherosclerosis and the use of cigarettes and alcohol. An autopsy study. New England Journal of Medicine 279(26):1413–1420, December 26, 1968.

(3) Avtandilov, G. G., Kolesova, V. I., Ponomarenko, O. V. Kurenie tabaka i stepen' ateroskleroticheskogo porazheniya koronarnykh arteriy serdtsa i aorty. (Tobacco smoking and the degree of atherosclerotic lesions of coronary arteries of the heart and aorta.) Kardiologiya 5(1):30–34, January–February 1965.

(23) Viel, B., Donoso, S., Salcedo, D. Coronary atherosclerosis in persons dying violently. Archives of Internal Medicine 122(2):97–103, August 1968.

Cigarette Smoking and Angina. The report of (1) Aronow et al. is based on 10 selected patients who have been trained on an ergometer. The shortening of exercise time before pain appeared following smoking was not seen on 8 occassions out of 40 times in 10 patients. There were no nonsmoking controls to show their variability for comparison and there was no indication of incidence of reactors to the test in a group of unselected anginal patients.

The calculation of tension-time index was calibrated in dogs. The modification introduced has not been checked in man to prove that the index represents myocardial oxygen. The manner of reasoning by the authors is reproduced as follows:

Discussion

The results of the present study indicate a significant relationship between cigarette smoking and the appearance, with less provocation, of angina pectoris in patients who have known coronary artery disease.

Well-known effects of smoking are increases in both blood pressure and heart rate (7). Indeed, all of the subjects in these studies developed increases in these parameters after smoking. The increase in heart rate and blood pressure is based upon the known increase in catecholamine discharge from the adrenal medulla and from chromaffin tissue in the heart that occurs during smoking (9–11). Nicotine is also known to act on chemoreceptors in the carotid and aortic bodies, reflexly causing acceleration of the heart rate and an increase in blood pressure (12). In addition, low concentrations of nicotine can stimulate sympathetic ganglion cells.

The product of blood pressure and heart rate has been found to be a good index for the oxygen cost of cardiac hemodynamic activity (13). Sarnoff and coworkers (14) have found the primary hemodynamic determinant of oxygen consumption of the heart to be the total tension developed by the myocardium (heart rate times the area under the systolic portion of the aortic pressure curve). Robinson (15) states, ". . . the precipitation of angina could be consistently related to the level reached by the product of heart rate and systolic blood pressure (corrected when necessary for changes in ejection time)." Using this index, it can be readily seen that smoking increases the oxygen consumption of the heart.

Patients with coronary heart disease increase the myocardial demand for oxygen when they exercise. The present study indicates that this increase is even greater when the exercise is preceded by smoking. In such instances, patients with coronary disease cannot meet the increased demands for myocardial oxygen. Therefore, there is a decreased amount of time between the performance of exercise and the onset of angina after smoking.

Kjeldsen, et al. (15) compared the vascular pathology in rabbits fed a high cholesterol diet and maintained in an hypoxic atmosphere (10 percent oxygen) with that in rabbits exposed only to the high cholesterol diet. The authors demonstrated that hypoxia leads to an increase in the degree of plaque formation in the coronary arteries and in the amount of visible aortic atheromatosis, as well as to an increase in the aortic content of cholesterol and triglycerides. In addition, the hearts of the hypoxic animals showed marked perivascular xanthomatosis, often infiltrating the surrounding myocardium. In summarizing this experiment and their previous findings of increased atheromatosis in hypercholesterolemic rabbits subjected to high carboxyhemoglobin (COHb) levels, the authors (2) state that tissue hypoxia seems to be an important factor in initiating these lesions, regardless of the manner in which the hypoxia is produced. Although the COHb levels in the rabbits and the degree of hypoxia were much higher than that experienced by human smokers, these results suggest a mechanism by which smoking might contribute to atherosclerosis.

Hass, et al. (12), extending studies reviewed in the 1968 Report (27), have demonstrated that the administration of injections of nicotine to hypercholesterolemic rabbits who are also given vitamin D enhances the peripheral atheromatous calcific arterial disease which is produced by the combination of hypercholesterolemia and vitamin D administration. The addition of nicotine to the regimen also resulted in the frequent occurrence of thromboarteritis in the distal calcified arteries of cardiac and skeletal muscle, and of the smooth muscle of the gastrointestinal tract. The nicotine effect was reproduced by substituting appropriate dosages of adrenalin for nicotine and abolished by adrenalectomy.

Lellouch, et al. (16) have reported that the administration of a mono-amine oxidase (MAO) inhibitor to rabbits on a regimen of daily nicotine injections significantly reduced the number of animals who developed fibrotic lesions of the aorta in response to nicotine. Further work is in progress to elucidate the mechanism of the MAO effect.

Evidence presented in this and previous reports suggests that cigarette smoking promotes atherosclerosis.

Thrombus Formation and Blood Flow

Hess, et al. (13) discovered aggregations of platelets, erythrocytes fibrin, detached epithelial cells, and some as yet unidentified cells on the aortic and carotid walls of rabbits subjected to cigarette smoke

The discovery of a plasma factor which increases the *in vitro* synthesis of fibrinogen by human liver biopsies has been reported by Pilgeram, et al. (20) in older patients who have recovered from myocardial infarction. This factor has been tentatively identified as free fatty acid (FFA). The authors state that the association between FFA and fibrinogen synthesis may provide the link between hyperlipemia and clotting. Cigarette smoking causes an increase in FFA through its stimulation of catecholamine release.

Several recent studies have begun to elucidate the role which changes in blood viscosity and certain features of the microcirculation might play in the development of atherosclerosis and coronary heart disease.

Dintenfass (7) has suggested that myocardial infarction and coronary thrombosis may be the result of a number of factors, separate or interrelated, all leading to a high viscosity of the blood. These factors may affect the migration and adhesion of platelets, the volume of plasma, and the rigidity of the red blood cell. Phenomena leading to high blood viscosity may occur in focal areas leading to occlusion of small vessels, resultant ischemia, and an infraction of either subclinical or catastrophic proportions, depending on the location and number of vessels involved. Dintenfass also believes that an increase in blood viscosity precedes the clinical manifestations of the high blood viscosity syndrome and that the increased blood viscosity seen in post myocardial infarct patients is a reflection of the etiology rather than the effect of the disease.

Local hypoxia leading to an increase in the rigidity of the blood cell might be produced by cigarette smoking through the increase in COHb. Platelet adhesiveness is increased by smoking, probably secondary to the release of catecholamines (27).

In a study of 50 white males with myocardial infarcts and 40 controls, Stables, et al. (22) found that the patients with myocardial infarct had a mean hematocrit level significantly higher than that of the controls. Studies of blood volume indicated that a reduction in plasma volume rather than an increase in red cell mass among the myocardial infarct patients accounted for the elevated hematocrit.

(15) Kjeldsen, K., Wanstrup, J., Astrup, P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 8(5) : 837–845, 1968.

(2) Astrup, P., Kjeldsen, K., Wanstrup, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7 : 343–354, 1967.

(12) Hass, G., Henson, D., Langerholm, W., Hemmens, A. Prevention of nicotine induction of atherocalcific thromboarteritis in rabbits. Circulation 38 (4, Supplement 6) : 8, October 1968.

(16) Lellouch, J., Jacotot, B., Angtera, G., Grosgogeat, J., Beaumont, J.-J. Action chronique de la nicotine sur l'intima aortique du lapin. Influence d'un inhibiteur de la mono-amine oxydase (I.M.A.O.) Journal of Atherosclerosis Research 5(1) : 137–142, January/February 1965.

(13) Hess, H., Frost, H. Rauchen und arterielle Verschlusskrankheiten. Fortschritte der Medizin 86(19) : 841–843, October 10, 1968.

(20) Pilgeram, L. O., Pickart, L. R. Control of fibrinogen biosynthesis: The role of free fatty acid. Journal of Atherosclerosis Research 8 : 155–161, 1968.

(7) Dintenfass, L. Blood rheology in pathogenesis of the coronary heart diseases. American Heart Journal 77(1) : 139–147, January 1969.

(22) Stables, D. P., Rubenstein, A. H., Metz, J., Levin, N. W. The possible role of hemoconcentration in the etiology of myocardial infarction. American Heart Journal 73(2) : 155–159, February 1967.

Vitamins and atherosclerosis. The introduction of Vitamin D into the investigation of atherosclerosis raises the question of the role of other vitamins. Spittle subsequently wrote a letter to the Editor of Lancet (April 8, 1972), recalling the long association between Vitamin C and atherosclerosis.

ATHEROSCLEROSIS AND VITAMIN C

SIR,—Dr. Morin (March 11, p. 594) feels that I may be overoptimistic in attributing[9] the rise in serum-cholesterol after vitamin C in patients with atherosclerosis to arterial mobilisation, and that perhaps there is a potential danger in the administration of large doses of vitamin C.

It is of interest that my first observations were made with fruits and vegetables, before I realised that the active agent was vitamin C. Even with these much smaller quantities of vitamin C, I was able to produce the same effects. It was with healthy older people on a vitamin-C-rich diet that I first saw the rise in level which led me to investigate the patients. It is true that many of the patients were having other therapy as well as vitamin C, but this cannot be said of the healthy subjects.

There are some features which add very strong supportive evidence to my conclusion that vitamin C is the only factor involved in atherosclerosis.

Carnivorous animals do not have atherosclerosis, and they synthesise their own vitamin C. It is possible to give them atherosclerosis without giving a deliberately atherogenic diet. This has happened in the Philadelphia Zoological Gardens.[10] Lesions were noticed about five years after the introduction of improved diets for the animals. This is the only instance that I am aware of which compares with the fate of the human who embarks on a "westernised" diet, and it shows that animals behave in the same way as humans when the balance between vitamin C and fats is disturbed.

There is a seasonal variation in deaths from myocardial infarction,[11] which coincides with our maximum and minimum consumption of vitamin C.

Two standard measures are advocated for all coronary patients in the interests of preventing a further attack; to give up smoking and to lose weight. Both these measures increase the available vitamin C—the second by its abundance in a low-calorie diet.

Recently, I did a necropsy on a man who had been in a mental hospital since the age of 12 years. He had been having vitamin supplements since admission. He died at the age of 62 years, from drowning. His arteries were clean.

I should like to emphasise again that Sokoloff[12] in his series had no recurrence of myocardial or cerebral infarction with vitamin-C treatment in 2½ years, and he states that 50 of his 60 patients were a lot better. This, surely, is consistent with an arterial "decoke".

We should start a large-scale trial of this substance in patients with atherosclerosis.

Pinderfields General Hospital,
Aberford Road,
Wakefield, Yorkshire.

CONSTANCE R. SPITTLE.

Fibrinogen Synthesis. The paragraph is written as though (2) Pilgeram and Pickart associated their Results with cigarette smoking. The association was added by somebody else. There is no mention of cigarette smoking in Pilgeram and Pickart's article. Note that the transposition of results is increasing by one step as follows: cigarette smoking ⟶ release of epinephrine ⟶ elevation of FFA ⟶ fibrinogen synthesis ⟶ clotting ⟶ atherosclerosis.

DISCUSSION

A role for FFA in the turnover of fibrinogen could have been predicted by the correlation of a number of earlier studies. For example, incorporation of glycine into fibrinogen is enhanced by epinephrine[5,9]. However, epinephrine is well known to mobilize FFA[10]. ACTH has been reported to raise the plasma content of fibrinogen[11,12]. ACTH administration has been shown to induce elevation in plasma FFA and to induce thrombosis[13]. Chronic stress syndromes have been associated with elevations in plasma fibrinogen[14-16]. However stress has also been found to induce an output or increase of epinephrine, cholesterol, and FFA[17-20]. Stress has also been associated with myocardial infarction or coronary thrombosis[21]. Cortisone, depending upon dosage, induces an increase in fibrinogen[22] or a decrease[23]. Cortisone also restores the mobilization of FFA in adrenalectomized animals exposed to trauma[10], etc.

Correlation of a number of reports also suggests a role for FFA in the formation of fibrin or fibrinogen-fibrin intermediates. Saturated long chain fatty acids shorten the clotting time and accelerate thrombus formation[24-27], activate Hageman factor[28], aggregate platelets[29], activate plasma thromboplastin antecedent[30], and induce thrombosis *in vivo*[27]. Although the clot promoting effect of FFA has been confirmed by a number of investigators, a failure of the fatty acid salt to accelerate the clotting of native plasma *in vitro*, *i.e.*, plasma that had not been decalcified, has been reported[30]. On the basis of this study, the authors concluded that it seemed doubtful that FFA are of importance in the development of intravascular thrombi. However, this con-

clusion requires reexamination in view of the study which showed that thrombi were induced *in vivo* by the infusion of fatty acid salts[27]. In these latter experiments the fatty acid salt entered into native plasma and still induced thrombi. From these considerations and from the data reported in this paper, it would appear warranted to suggest that FFA not only control the rate of synthesis or turnover of the soluble precursor of the clot forming protein, fibrin, but also play a significant role in determining the rate of formation of fibrin or precursors thereof. The enhanced rate of turnover of fibrinogen[4] is indicative of both an increase in the rate of biosynthesis and an increase in utilization. Study of the turnover rate does not in itself show the nature of the enhanced pathways of utilization. It is therefore pertinent to consider those reports which bear upon the nature of the pathway(s) of utilization of fibrinogen which are enhanced by FFA. The correlation of an enhanced turnover rate of fibrinogen with coronary thrombosis[4] and with changes in blood clotting indices, which are indicative of enhanced generation of thrombin, is suggestive of an increase in the formation of fibrin or fibrinogen–fibrin intermediates. For example, enhanced generation of plasma thromboplastin[31,32] and a deficiency in plasma antithromboplastin[33] are found in thrombotic complications. An enhanced level of antithrombin[34], possibly a protective feed-back mechanism against thrombin, is found in coronary thrombosis. An increased concentration of plasma fibrinogen is also found in coronary thrombosis[1,4,31]. This increase has been shown to correlate with the enhanced rate of biosynthesis and utilization[4]. Our recent study, which shows that thrombin induces, *in vivo*, a significant increase, up to 1.9-fold, in the rate of biosynthesis of fibrinogen[35] suggests that the enhanced rate of turnover reflects conversion of fibrinogen to fibrin. These correlations are made with an awareness that the platelets play an important role in the formation of thrombi. However, it has been recently shown that platelets will not clump unless fibrinogen is present[36]. The role of fibrinogen, fibrin, and thrombin in the clumping and utilization of platelets was recently reviewed[37]. The fact that thrombin not only enhances the turnover of platelets but also the turnover of fibrinogen[4] combined with the observations that both the turnover of platelets[38] and the turnover of fibrinogen[4] are enhanced in coronary artery disease suggests that conversion to fibrin is a significant pathway in the enhanced turnover of fibrinogen.

A control by FFA over the metabolism of fibrinogen may have implications with respect to unifying the two theories on atherogenesis which are based either on disturbed fat metabolism or on blood clotting. The intravascular deposition of fibrin-platelet thrombi has been implicated as a cause of arteriosclerosis since the time of Vos Rokitansky[39]. Numerous recent histological investigations show that thrombi on the vessel surfaces give rise to intimal thickening and eventually arteriosclerosis[40–47]. Recently, injections of thrombin into the areas of the intima and the media were shown to produce atheroma[48].

Carbon Monoxide

Several reviews of the pathophysiology of exposure to carbon monoxide (CO) have appeared recently. These are pertinent to the discussion of the relationship of smoking to health, since cigarette smoke contains amounts of CO sufficient to cause a COHb level of 5 to 10 percent in the smoker, depending on the amount smoked and degree of inhalation (*2, 10*).

Bartlett (*4*) has pointed out that because the absorption of CO from the ambient environment is dependent upon the concentration of CO in the environment as contrasted to that in the blood, smokers with a COHb level of 5 percent will not absorb CO from inspired air unless the concentration of CO in the air exceeds 30 parts per million. However, he also states that because the excretion of CO between cigarettes will be lower in CO polluted air, the smoker will have a higher long-term average COHb level in a polluted environment. Patients with heart disease may be particularly susceptible to the hypoxic burden caused by the presence of COHb.

Goldsmith, et al. (*10*) have stated that for the U.S. urban population, cigarette smoking is probably the most important cause of increased COHb above the endogenous level produced by heme catabolism, followed by automobile exhaust, occupational sources, and home heating and cooking devices, in that order.

Although Dinman (*6*) minimizes the importance of the effect of CO levels of 5 to 10 percent on the myocardium, he states that a shortcoming in his approach is that focal areas of myocardial ischemia are not reflected in the determination of oxygen saturation made from samples of blood taken from the coronary sinus. Such areas of ischemia might be important in initiating fatal arrhythmias. Levels of COHb which decrease further the oxygen supply to the ischemic myocardium might be readily provided by cigarette smoking.

Eliot, et al. (*3*) have reported effects of cigarette smoking on the oxygen affinity of hemaglobin independent of the presence of CO. Their results suggest that cigarette smoking may have both acute and chronic effects on oxygen affinity which differ in direction. The authors caution, however, that the *in vivo* oxygen affinity of hemoglobin may be different from that implied by the static equilibrium data. Further research is in progress.

(2) Goldsmith, J. R. Carbon monoxide. Science 157: 842–844, August 18, 1967.

(10) Goldsmith, J. R., Landaw, S. A. Carbon monoxide and human health. Science 162(3860): 1352–1359, December 20, 1968.

(4) Bartlett, D., Jr. Pathophysiology of exposure to low concentrations of carbon monoxide. Archives of Environmental Health 16(5): 719–727, May 1968.

(6) Dinman, B. D. Pathophysiologic determinants of community air quality standards for carbon monoxide. Journal of Occupational Medicine 10(9): 446–463, September 1968.

(3) Eliot, R. S., Steiff, R., Salhany, J. M., Mizukami, H. Personal Communication. April 1969.

The Health Consequences of Smoking

A Report of the Surgeon General: 1971

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

Contents

FIGURES

LIST OF TABLES

(A indicates tables located in Appendix at end of Chapter)

INTRODUCTION

Coronary Heart Disease (CHD) cuts short the lives of many men in the Western World in their prime productive years. More Americans die from heart disease than from any other disease. In 1967, in this country, a total of 345,154 men and 227,999 women were classified as dying of arteriosclerotic heart disease (ASHD) (*196*), a category which consists largely of what is commonly called CHD. During the years from 1950 to 1967, the age-adjusted death rate from ASHD increased 15.1 percent (*196, 197*).

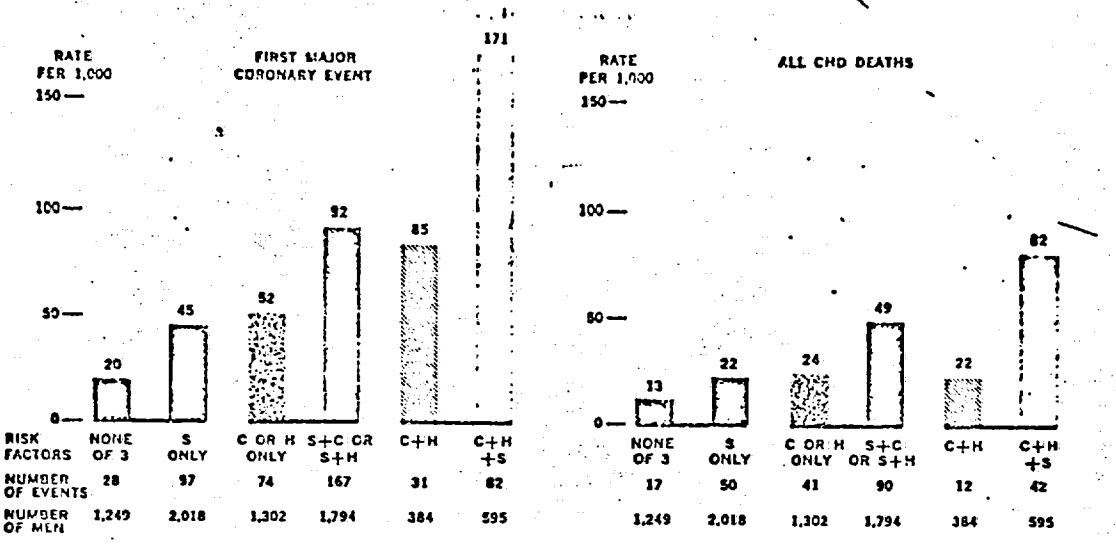
Besides the many deaths attributed to CHD, much morbidity results from this disease. The National Health Examination Survey of 1960–1962 estimated that 3.1 million American adults, ages 18 to 79, had definite CHD and 2.4 million had suspect CHD, together representing about 5 percent of the population. It was further estimated that of Americans under age 65, almost 1.8 million had definite CHD and 1.6 million had suspect CHD (*195*).

There are several manifestations of CHD, all related in part to the basic process of severe atherosclerosis, a disease of arteries in which fatty materials (lipids) accumulate in the form of plaques in the walls of medium and large arteries. This process, as it occurs in the coronary arteries, leads to stiffening of the wall and narrowing of the lumen which, when severe, result in a diminution in the blood supply to the cardiac muscle. Angina pectoris, a major manifestation of CHD, results from diminution in blood supply relative to the needs of the myocardium. If the blood supply to a portion of the myocardium is completely obstructed, due for example to the formation of a thrombus at the site of atherosclerotic narrowing, necrosis or death of a portion of heart muscle may occur. This occurrence is known as a myocardial infarction. In many cases, a disturbance of cardiac rhythm occurs at the time of thrombosis, and the patient may die immediately. It is estimated that approximately 25 percent of patients suffering coronary artery occlusion die within the first three hours following the occlusion (table 1) (*88*). Not infrequently, sudden death occurs in patients with severe coronary atherosclerosis but without a demonstrable arterial occlusion. In these cases, it is thought that the meager blood flow to a portion of the myocardium becomes so diminished with respect to cardiac needs as to lead to a fatal arrhythmia, as well as to, perhaps, a myocardial infarction.

(196) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HE... STATISTICS. Vital Statistics of the United States—1967, Vo... Mortality, Part A. Washington, U.S. Department of Health, ... tion and Welfare, Public Health Service Publication. 1969.

(197) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEA... STATISTICS. Vital Statistics Rates in the United States 19... Washington, U.S. Department of Health, Education and We... Public Health Service Publication No. 1677, 1968. 881 pp.

(195) U.S. PUBLIC HEALTH SERVICE. NATIONAL CENTER FOR HEA... STATISTICS. Vital and Health Statistics. Data from the N... Health Survey. Coronary Heart Disease in Adults—United S... 1960–1962. Washington, U.S. Department of Health, Educatio... Welfare, National Center for Health Statistics Series 11, N... September 1965. 46 pp.



National Cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for first major coronary event (incling nonfatal MI, fatal MI, and sudden death due to CHD) and any coronary death. U.S. white males age 30–59 at entry. All rates age-adjusted by 10-year age groups to the U.S. white male population 1960. Graphs present rates for noncigarette vs. cigarette smokers at entry with simultaneous control of blood pressure and serum cholesterol level. For this latter analysis, the following cutting points were used:

(a) Cigarette smoking S —any use at entry
(b) Serum cholesterol C — 250 mg./dl.
(c) Diastolic blood pressure H — 93 mm. Hg.

SOURCE: Inter-Society Commission for Heart Disease Resources. National Cooperative Pooling Project Data (88).

FIGURE 1—National Cooperative Pooling Project; smoking status at entry and 10-year age-adjusted rates per 1,000 men for first major coronary event (includes nonfatal MI, fatal MI, and sudden death due to CHD) and any coronary death. U.S. white males age 30–59 at entry. All rates age-adjusted by 10 year age groups to the U.S. white male population 1960. Graphs present rates for noncigarette vs. cigarette smokers at entry with simultaneous control of blood pressure and serum cholesterol level. For this latter analysis, the following cutting points were used:

(a) Cigarette smoking—S–any use at entry
(b) Serum cholesterol—C–≧250 mg./dl.
(c) Diastolic blood pressure—H–≧90 mm. Hg.

SOURCE: Inter-Society Commission for Heart Disease Resources. National Cooperative Pooling Project Data (88).

TABLE 1.—*Sudden death and acute mortality with first major coronary episodes*

Author, year, country, reference	Number and type of population	Data collection	Event	Number of events	Proportion per 1,000 events (as calculated on the basis of age-adjusted rates)	Comment
Pooling Project, American Heart Association, 1970, U.S.A. (88).	7,324 males males 30–59 years of age at entry. Ten-year experience.	Medical examination and follow-up.	All first major coronary episodes, nonfatal and fatal.	601	1,000.0	Data from the Pooling Project, Council on Epidemiology, American Heart Association, a national cooperative project for pooling data from the Albany civil servant, Chicago Peoples Gas Co., Chicago Western Electric Co., Framingham Community, Los Angeles civil servant, Minneapolis-St. Paul business men, and other prospective epidemiologic studies of adult cardiovascular disease in the United States.
			Sudden death (death within 3 hours of onset of acute illness).	123	245.5	
			All acute deaths with first episodes.	165	329.3	

SOURCE: Inter-Society Commission for Heart Disease Resources (88). Representative references include: (54, 96, 148, 177) and others listed as 6a–6k in Inter-Society Commission for Heart Disease Resources report.

(88) INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES. Atherosclerosis Study Group and Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42(6): A-54–A-95, December 1970.

(54) DOYLE, J. T., DAWBER, T. E., KANNEL, W. B., KINCH, S. H. KAHN, H. A. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, N.Y., and Framingham, Mass., studies. Journal of the American Medical Association 190(10): 886–890. December 7, 1964.

(96) KANNEL, W. B., CASTELLI, W. P., MCNAMARA, P. M. Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis. The Framingham study. IN: Wynder, E. L., Hoffmann, D., (Editors). Toward a Less Harmful Cigarette. Bethesda, U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute Monograph No. 28, June 1968. pp. 9–20.

(148) PAUL, O., LEPPER, M. H., PHELAN, W. H., DUPERTUIS, G. W., MACMILLAN, A., MCKEAN, H., PARK, H. A longitudinal study of coronary heart disease. Circulation 28(1): 20–31, July 1963.

(177) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOSONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. Archives of Environmental Health 13(3): 322–335, September 1966.

TABLE 2.—*Coronary heart disease mortality ratios related to smoking—prospective studies*

(Actual number of deaths shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Cigars, pipes	Age variation	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 8 states 50–63 years of age.	Questionnaire and follow-up of death certificate.	3½	8,297	NS .....1.00 (709) All smokers .1.70 (3361) <10 .....1.29 (192) 10–20 ....1.89 (864) 20–40 ....2.20 (604) >40 .....2.41 (118)	*Cigars* NS..1.00 SM..1.28 (420) *Pipes* NS..1.00 SM..1.03 (312)	*50–54* *55–59* *60–64* *65–69* NS .....1.00 (90) 1.00 (142) 1.00 (294) 1.00 (278) All smokers .1.93 (765) 1.85 (962) 1.46 (721) 1.41 (715) <10 .....1.38 (35) 1.38 (50) 1.17 (62) 1.27 (68) 10–20 .....2.00 (213) 2.04 (258) 1.31 (235) 1.58 (159) >20 .....2.51 (203) 2.47 (193) 1.92 (129) 1.56 (73)	[1] ($p<0.001$)
Doyle et al., 1964, U.S.A. (64).	2,282 males, Framingham, 30–62 years of age. 1,913 males, Albany, 39–55 years of age.	Detailed medical examination and follow-up.	10 8	93	NS .....1.00 (20) All smokers .2.40 (73) <20 .....2.00 (17) 20 .....1.70 (20) >20 .....2.50 (36)			Data apply only to males aged 40–49 and free of CHD at entry. NS include pipe, cigar and ex-smokers.
Doll and Hill, 1964, Great Britain (50).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	1,376	NS .....1.00 All smokers .1.35 1–14 ....1.29 15–24 ....1.27 >25 .....1.43		*35–44* *45–64* *65–84* NS .....1.00 1.00 1.00 1–14 .....1.73 1.40 1.71 15–24 .....4.45 1.73 1.27 >25 .....1.86 1.92 1.88	
Strobel and Gsell 1965 Switzerland (180).	3,749 male Swiss physicians.	Questionnaire and follow-up of death certificate.	9	162	NS .....1.00 1–20 .....1.48 >20 .....1.76	NS..1.00 SM..1.45		
Best, 1966 Canada (24).	Approximately 78,000 male Canadian veterans.	Questionnaire and follow-up of death certificate.	6	2,000	NS .....1.00 All smokers .1.60 (1350) <10 .....1.55 (337) 10–20 .....1.58 (766) >20 .....1.78 (277)	*Cigars* NS..1.00 SM..0.95 (16) *Pipes* NS..1.00 SM..0.96 (95)	*50–69* *50–69* *70 and over* <10 .....0.87 (18) 1.56 (220) 1.71 (99) 10–20 .....1.45 (115) 1.67 (557) 1.29 (94) >20 .....1.85 (65) 1.76 (184) 1.73 (25)	
Kahn 1966 U.S.A. (89).	U.S. male veterans 2,265,674 person years.	Questionnaire and follow-up of death certificate.	8½	10,830	NS .....1.00 (2397) All smokers .1.74 (4150) 1–9 .....1.39 (439) 10–20 .....1.78 (2102) 21–39 .....1.81 (1292) >39 .....2.00 (266)	*Cigars* NS..1.00 SM..1.04 (623) *Pipes* NS..1.00 SM..1.08 (336)		
Hirayama, 1967, Japan (84).	265,118 Japanese adults over age 40.	Trained interviewers and follow-up of death certificate.	1	61	NS .....1.00 (17) 1–24 .....1.13 (69) >25 .....1.00 (8)			Preliminary report.
Kannel et al., 1968, U.S.A. (94).	5,127 males and females age 30–59.	Medical examination and follow-up.	12	62	NS .....1.00 (27) SM>20 ....2.20 (25)			[1] ($p<0.05$)

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

[1] "p" values specified only for those provided by authors.

(77) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. I. Total mortality. Journal of the American Medical Association 166 (10): 1159–1172, March 8, 1958.

(78) HAMMOND, E. C., HORN, D. Smoking and death rates—report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. Journal of the American Medical Association 166(11): 1294–1308, March 15, 1958.

(50) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. (Part I) British Medical Journal 1(5395): 1399–1410, May 30, 1964.

(180) STROBEL, M., GSELL, O. Mortalität in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Ärzten in der Schweiz. (Mortality in relation to tobacco smoking. Nine years of observation in Swiss doctors.) Helvetica Medica Acta 32(6): 547–592, December 1965.

(24) BEST, E. W. R. A Canadian Study of Smoking and Health. Ottawa, Department of National Health and Welfare, 1966. 133 pp.

(84) HIRAYAMA, T. Smoking in relation to the death rates of 265,118 men and women in Japan. National Cancer Center, Research Institute. Tokyo, September 1967. 14 pp.

TABLE 2.—*Coronary heart disease mortality ratios related to smoking—prospective studies (cont.)*

(Actual number of deaths shown in parentheses)*

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day	Males	Females	Cigars, pipes	Age variation	Comments
Hammond and Garfinkel, 1969, U.S.A. (76).	359,534 males 445,878 females age 40–79 at entry.	Questionnaire and follow-up of death certificate.	6	14,819	NS 1–9 10–19 20–30 >30	1.00 1.27 1.60 1.78 1.77	1.00 0.84 1.22 1.52 0.61		Males 40–49: NS 1.00; 1–9 1.60; 10–19 2.59; 20–30 3.76; >40 6.61 50–59: NS 1.00; 1–9 1.59; 10–19 2.13; 20–30 2.40; >40 2.79 60–69: NS 1.00; 1–9 1.48; 10–19 1.82; 20–30 1.91; >40 1.73 70–79: NS 1.00; 1–9 1.14; 10–19 1.41; 20–30 1.49; >40 1.47 Females 40–49: NS 1.00; 1–9 1.31; 10–19 2.05; 20–30 3.52; >40 †3.31 50–59: NS 1.00; 1–9 1.15; 10–19 2.37; 20–30 2.63; >40 3.73 60–69: NS 1.00; 1–9 1.06; 10–19 1.79; 20–30 2.08; >40 †2.02 70–79: NS 1.00; 1–9 0.76; 10–19 0.98; 20–30 1.27; >40 —	†Based on 5–9 deaths.
Paffenbarger and Wing 1969 U.S.A. (146)	50,000 male former students.	Baseline interview and examination and follow-up by death certificate.	17–51	1,145 matched with 2,292 controls	NS SM	1.00 1.50	(385)	(p<0.01)	50–54: NS 1.00; SM 1.50 (88) 55–59: NS 1.00 (p<0.01); SM 1.60 (163) 60–64: NS 1.00; SM 1.20 (134)	
Paffenbarger et al., 1970, U.S.A. (144).	3,263 male longshoremen 35–64 years of age.	Initial multiphasic screening and follow-up of death certificate.	16	291	NS and <20 SM >20	1.00 2.08	(137) (154)	(p<0.01)		
Taylor et al., 1970, U.S.A. (113).	8,571 male railroad employees 40–59 years of age at entry.	Interviews and regular follow-up examination.	5	48	NS <20 >20	1.00 1.97 3.60	(4) (20) (22)			Data apply only to those free of CHD at entry.
Weir and Dunn, 1970, U.S.A. (105).	68,153 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	1,718	NS All smokers ±10 ±20 >40	1.00 1.60 1.39 1.67 1.74			55–64: NS 1.00; ±10 4.22; ±20 6.14; ±30 8.57; >40 7.93; All 6.24 45–54: NS 1.00; ±10 2.05; ±20 3.17; ±30 3.83; >40 3.16; All 2.96 55–64: NS 1.00; ±10 1.41; ±20 1.64; ±30 1.66; >40 1.42; All 1.56 65–69: NS 1.00; ±10 1.17; ±20 1.26; ±30 1.36; >40 1.42; All 1.24	NS includes pipes and cigars. SM includes ex-smokers.
Cooperating Project, American Heart Association, 1970, U.S.A. (18).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	10	239	NS <10 20 >20	1.00 1.66 1.70 3.00	(27) (34) (56) (68)	1.00 (27) 1.20 (24)		

* Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion either occasional, mixed

(146) PAFFENBARGER, R. S., JR., WING, A. L. Chronic disease in former college students. X. The effects of single and multiple characteristics on risk of fatal coronary heart disease. American Journal of Epidemiology 90(6): 527–535, December 1969.

(144) PAFFENBARGER, R. S., JR., LAUGHLIN, M. E., GIMA, A. S., BLACK, R. A. Work activity of longshoremen as related to death from coronary heart disease and stroke. New England Journal of Medicine 282(20): 1109–1114, May 14, 1970.

(105) WEIR, J. M., DUNN, J. E., JR. Smoking and mortality: A prospective study. Cancer 25(1): 105–112, January 1970.

Longshoremen Study. Another interpretation to the report of (144) Paffenbarger et al. is raised in the Letter to the Editor by Chretien (N Engl J Med 283: 100, 1970). The answer by Paffenbarger is also reproduced below.

OCCUPATIONAL PRESELECTION

To the Editor: The recent study of longshoremen by Paffenbarger et al. (NEJM 282:1109-1113, 1970) attributes the higher coronary rate in sedentary workers than in cargo handlers to differences in work activity, even after the influences of blood pressure and cigarette smoking are taken into account.

Similar studies in Great Britain among bus drivers[1] and postal workers[2] have uncovered a confounding factor — men who are initially taller and heavier for a given height select the more sedentary jobs.

Do the authors have any such information about the longshoremen?

JANE HENKEL CHRETIEN, M.D.
Student
Harvard School of Public Health
Boston, Mass.

1. Morris JN, Heady JA, Raffle PAB: Physique of London busmen — epidemiology of uniforms. Lancet 2:569-570, 1956
2. Oliver RM: Constitutional differences between men recruited for driving and non-driving occupations. Brit J Indust Med 26:289-293, 1969

The above letter was referred to the authors of the article in question, one of whom offers the following reply:

To the Editor: Essentially all longshoremen entered their industry as cargo handlers, performing strenuous, work-day tasks in the ship's hold, at dockside and in the warehouse for a minimum of five years. Men who shifted to physically less demanding jobs, which carry higher pay scales and greater authority, had compiled an adequate work record and seniority status. They shifted after an average of ab 13 years as cargo handlers.

Table 1. Mean Body Height and Weight Levels of Longshoremen According to Physical Activity of Work and Age at Initial Examination.

Age (Yr) in 1951	More Active Workers	Less Active Workers
	Mean Height (in)	Mean Weight (in)
35-44	68.9	68.9
45-54	68.1	68.3
55-64	67.6	67.7
Average	68.3	68.3
	Mean Weight (lb)	Mean Weight (lb)
35-44	180.6	185.6
45-54	178.3	179.8
55-64	177.9	180.2
Average	179.0	181.4
Adjusted for age & height*	179.1	181.2

Table 1, which gives a cross-section of the study popu tion in 1951, shows no difference in height between m and less active workers, with the less active averaging g (2 lb) heavier in weight. Although the relative height the two groups were similar, data are not yet available their relative weights at the time one group shifted to requiring less physical activity.

In the 16-year follow-up period afforded to study, death fr from coronary heart disease were 55 per 10,000 person ye experience for longshoremen who were physically active lean, 59 for those less active and lean, 64 for the active fat, and 99 for the less active and fat. This represents a p tentiating effect on coronary mortality from job-related phy ical inactivity and heavier weight for height.

Questions similar to Dr. Chretien's can be asked for oth high-risk factors. For example, do longshoremen with high blood-pressure levels seek out physically less active jobs? cigarette smokers? Such questions invited the analyses sho in Figure 6 of our paper (N.E.J.M. 282:1109-1114, 19 which surveyed coronary death rates for all paired combi tions of four high-risk factors. It showed more than an ad lapping influence, indicating at least partial independence the factors on coronary mortality. Each of the six possi pairings of high-risk factors increased longshoremen's risk coronary death by more than additive amounts over the ri in the absence of the pair.

RALPH S. PAFFENBARGER, JR., MD
(D
Bureau of Adult Health and Chronic Disea
California St
Department of Public Hea
Berkeley, Cali

TABLE 3.—*Sudden death from coronary heart disease related to smoking*

(Mortality ratios—actual number of deaths shown in parentheses)

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes/day	Cigars, pipes	Comment
Pooling Project, American Heart Association, 1974, U.S.A. (61).	7,427 white males 35–59 years of age at entry.	Medical examination and follow-up.	10	145	Never smoked ....1.00 (16) ≤10 ....1.96 (27) 20 ....1.98 (60) >20 ....3.86 (44)	1.00 (15) 1.26 (13)	See table 1 for description of Pooling Project.

TABLE 4.—*Coronary heart disease morbidity as related to smoking*

(Risk ratios—actual number of CHD manifestations shown in parentheses[1]

SM = Smokers NS = Nonsmokers

EX = Ex-smokers)

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Pipes, cigars	Age variation	Comments
Doyle et al., 1964, U.S.A. (64).	2,282 males Framingham, 30–62 years of age. 1,913 males Albany, 30–65 years of age.	Detailed medical examination and follow-up.	10	243 myocardial infarctions and CHD deaths.	NS ....1.00 (62) All smokers ....2.36 (191) <20 ....1.95 (44) 20 ....2.85 (66) >20 ....3.04 (53)			Data include CHD deaths only on males 40–49 years of age and free of CHD on entry. NS includes pipes, cigars, and ex-smokers.
Seamer et al., 1966, U.S.A. (277).	1,329 CHD-free male employees of Peoples Gas Company 40–59 years of age.	Interview and examination with clinic follow-up.	4	46 CHD	NS ....1.00 (8) <10 cigarettes, < 5 cigars, < 5 pipes ....2.92 (6) 10–19 cigarettes ....3.67 (8) >20 cigarettes, > 5 cigars, > 5 pipes 3.33 (29)			NS includes ex-smokers. Includes all CHD.
Epstein, 1967, U.S.A. (61).	6,545 male and female residents of Tecumseh, Mich.	Initial medical examination and repeat follow-up examinations.	4	96 male, 92 female CHD including deaths, angina, and myocardial infarctions.	*Males* NS ....1.00 (1) EX ....4.33 (10) Cigarettes ....3.20 (26) *Females* NS ....1.00 (21) EX ....0.89 (1) Cigarettes 1.02 (14)	*Males—Continued* *60 and over* 1.00 (7) 1.27 (11) 1.56 (23) *Females—Continued* 1.00 (47) 1.81 (6) 6.42 (2)	*Males* *40–59* SM ....1.93 (2) *60 and over* SM 0.86 (4)	Reexamination of patients was spread over 1½–6-year period, but data are reported in terms of 4-year incidence rates. Actual number of CHD incidents derived from data on incidence and total in smoking class.

[1] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(61) EPSTEIN, F. H. Some uses of prospective observations in the Tecumseh Community Health Study. Proceedings of the Royal Society of Medicine 60(1): 4–8, January 1967.

Table 4.—*Coronary heart disease morbidity as related to smoking (cont.)*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[1]
[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day		Pipes, cigars	Age variation	Comments
..emhiar, et al., 1966, U.S.A. (90).	3,182 males 39-59 years of age at entry.	Initial medical examination and follow-up by repeat examinations.	4½	104 myocardial infarctions.	NS ....1.00 (21) EX ....2.47 (15) Current ....2.78 (63) 0-16/day ....†1.33 (43) >16 ....3.06 (69)	(p<0.001) (p<0.001) (comparing 0-16 and 16+)		30-49 / 50-59 NS....1.00 (4) 1.00 (4) Current 4.23 (35) 2.26 (33)	†Includes nonsmokers and ex-smokers. NS includes former pipe and cigar smokers.
..annel, et al., 1966, U.S.A. (84).	5,127 males and females 30-59 years of age.	Medical examination and follow-up.	12	225 myocardial infarctions. 380 CHD.	*Myocardial infarction* *Males* NS ....1.00 (21) All SM ....1.51 (153) Heavy SM ....1.85 (53) *Risk of CHD (overall)* *Males* NS ....1.00 (61) 1-10 ....1.24 (25) 11-20 ....1.89 (90) >20 ....2.41 (76)	*Myocardial infarction*—Continued *Females* 1.00 (11) 1.71 (23) *Risk of CHD (overall)*—Continued *Females* 1.00 (59) 0.86 (18) 1.20 (18) 0.83 (3)			
...Shapiro et al., 1969, U.S.A. (178).	110,000 male and female enrollees of Health Insurance Plan of Greater New York (HIP) 35-64 years of age.	Baseline medical interview and examination and regular follow-up.	5	Total unspecified.	*Males* NS ....1.00 All current ....2.14 cigarettes (p<0.01) <20 ....1.80 >20 ....2.33 >40 ....6.26	*Females* 1.00 2.00 (p>0.01) 1.77 6.93	*Males only* NS ....1.00 SM ....1.82 (p<0.01)	*Males* 35-44 45-54 55-64: 1.00 1.00 1.00; 2.47 3.06 1.69; 0.58 2.15 1.32; 3.04 3.23 1.81; 10.00 7.40 5.30 *Females* 35-44 45-54 55-64: 1.00 1.00 1.00; 2.35 2.37 1.80; 1.23 2.21 1.45; 20.25 11.75 4.07	Total myocardial infarction includes those dead within 48 hours. NS include ex-smokers.
Keys 1970 Yugoslavia Finland Italy Netherlands Greece (211).	9,184 males in 5 countries 40-59 years of age at entry.	Interviews and regular follow-up examination by local physicians.	5	65 deaths. 90 myocardial infarctions. 120 angina pectoris. 155 other. †428 total.	NS, EX (SM <20) ...1.00 (305) All current (>20) 1.33 (103)				Includes all CHD incidence including ECG diagnoses. Covers all countries investigated except U.S.A. † Difference between total CHD and the sum of smoking groups is due to difference in figures presented by authors.

[1] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

1005050710

TABLE 4.—*Coronary heart disease morbidity as related to smoking (cont.)*

(Risk ratios—actual number of CHD manifestations shown in parentheses)*
(SM = Smokers NS = Nonsmokers EX = Ex-smokers)

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day
Taylor, et al. 1970 U.S.A. (183).	2,471 male railroad employees 40–59 years of age at entry.	Interviews and regular follow-up examination.	6	46 deaths. 33 myocardial infarctions. 78 angina pectoris. 86 other CHD. 212 total.	NS and EX ....1.00 (62) All current 1.77 (150)
Dayton et al. 1970, U.S.A. (48, 49).	422 male U.S. veterans participating as controls in a clinical trial of a diet high in unsaturated fat.	Interviews and routine follow-up examinations.	up to 8	27 sudden deaths. 44 definite myocardial infarctions.	<10 .....1.00 (75) 10–20 .....1.04 (22) >20 .....1.17 (13)
Dunn et al. 1970 U.S.A. (66).	13,145 male patients in periodic health examination clinics.	Data only on new incidents extracted from clinic records.	up to 16	Total unspecified.	
Framingham Project, American Heart Association 1970, U.S.A. (69).	7,427 white males 30–59 years of age at entry.	Medical examination and follow-up.	16	538 Includes fatal and nonfatal myocardial infarction and sudden death.	Never smoked ..1.00 (62) <10 .....1.65 (72) 20 .....2.08 (305) >20 .....2.33 (154)
Paul et al., 1963, U.S.A. (166).	1,952 Western Electric Co. male workers participating in a prospective study for 4½ years.	Screening examination and history.			Coronary score (87) NS ..... 33 1–7 ..... 1 8–12 ..... 0 13–17 ..... 6 18–22 ..... 41 23–27 ..... 1 >28 5

PROSPECTIVE STUDIES—Continued

Pipes, cigars	Age variation	Comments
		All CHD including EKG diagnoses.
		No data on NS as a separate group.
	40–49 50–59 60–69 †Low SM 1.00(25) 1.00(125) 1.00(157) ‡High SM 2.17(10) 0.90 (31) 1.41 (53)	† Includes NS, EX, and <20 cigarettes/day. ‡ >20 cigarettes/day. Includes all CHD but excludes death. No data available comparing smokers and nonsmokers.
1.00(83) 1.25(84)		
Noncoronary controls (1,744) 33 7 11 13 39 2 0 (p<0.005)		88 developed clinical coronary disease, 47 angina pectoris, 28 myocardial infarction, 13 deaths CHD.

* Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of other occasional, miscellaneous, mixed, or ex-smokers.

(48) DAYTON, S., PEARCE, M. L. Diet and atherosclerosis. Lancet 1(7644): 473–474, February 28, 1970.

(49) DAYTON, S., PEARCE, M. L., HASHIMOTO, S., DIXON, W. J., TOMIYASU, U. A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis. Circulation 40(1 Supplement 11), July 1969. 63 pp.

(66) DUNN, J. P., IRSEN, J., ELSOM, K. O., OHTANI, M. Risk factors in coronary artery disease, hypertension and diabetes. American Journal of the Medical Sciences 259(5): 303–322, May 1970.

Diet and Atherosclerosis. The article of (48) Dayton and Pearce has provoked some comments from the authors (Lancet 28 February 1970).

DIET AND ATHEROSCLEROSIS

SIR,—The leading article (Nov. 1, p. 919) in which you discussed our trial of a diet high in unsaturated fat[1] made it clear that our report had not dealt adequately with at least one crucial question. Specifically, your article suggested that the low incidence of atherosclerotic events in participants on the experimental diet might have been due to the chance inclusion of a smaller number of heavy cigarette smokers in that group than in the control group. In order to satisfy ourselves and others on this point, we have undertaken further analysis of our results in relation to smoking habits. The results of this analysis, reported below, provide convincing evidence that differences in smoking habits could not have accounted for the favourable experience of subjects on the experimental diet.

We have examined the question by stratifying the subjects on the basis of cigarette-smoking habits as reported at the time of entry into the trial. The outcome experience of the control and experimental groups was then compared within each stratum. Incidence of the primary end-point (ischæmic heart-disease manifested by sudden death or by definite myocardial infarction) was expressed in terms of

1. Dayton, S., Pearce, M. L., Hashimoto, S., Dixon, W. J., Tomiyasu, U. American Heart Association Monograph no. 25. New York, 1969.

TABLE I—NUMBERS AND INCIDENCE-RATES OF MAJOR END-POINTS, STRATIFIED BY CIGARETTE-SMOKING HABITS AT ENTRY INTO THE TRIAL

Cigarette use at entry into study	Control group		Experimental group	
	No. of subjects	Incidence* per 100 man-years	No. of subjects	Incidence* per 100 man-years
Less than 10 cigarettes per day:				
No. of men in subgroup..	166	..	164	..
S.D. or M.I.	25	2·45	21	2·02
S.D., M.I., or C.I.	32	3·13	25	2·40
Any "hard" end-point†	32	3·13	27	2·60
Fatal atherosclerotic events	20	1·95	18	1·73
10–20 cigarettes per day:				
No. of men in subgroup..	129	..	173	..
S.D. or M.I.	22	2·56	20	1·76
S.D., M.I., or C.I.	30	3·49	21	1·85
Any "hard" end-point ..	34	3·95	25	2·20
Fatal atherosclerotic events	26	3·02	19	1·67
More than 20 cigarettes per day:				
No. of men in subgroup..	70	..	45	..
S.D. or M.I.	15	2·66	8	1·70
S.D., M.I., or C.I.	17	3·73	8	2·04
Any "hard" end-point ..	20	4·39	8	2·04
Fatal atherosclerotic events	16	3·51	8	2·04
Not known:				
No. of men in subgroup	57	..	42	..
S.D. or M.I.	5	1·24	6	1·95
S.D., M.I., or C.I.	8	1·99	8	2·60
Any "hard" end-point ..	10	2·48	8	2·60
Fatal atherosclerotic events	8	1·99	5	1·62
All subjects:				
No. of men in group ..	422	..	424	..
S.D. or M.I.	65	2·57	57	1·87
S.D., M.I., or C.I.	87	3·18	60	2·16
Any "hard" end-point..	96	3·51	66	2·38
Fatal atherosclerotic events	70	2·55	48	1·73

* A man with more than one event at the category cited was counted once only.

† Includes those events cited in the preceding footnote, plus the following: interruption of an extremity due to ischæmic gangrene, ruptured aneurysm, arterial infection.

S.D. = sudden death due to ischæmic heart-disease.
M.I. = definite myocardial infarction (overt or silent).
C.I. = definite cerebral infarction.

TABLE II—ESTIMATED "SMOKING-ADJUSTED" INCIDENCE OF MAJOR END-POINTS FOR TOTAL STUDY POPULATION

Clinical incident	Adjusted number of subjects affected		Adjusted incidence per 100 man-years	
	Control	Exper.	Control	Exper.
S.D. or M.I.	65·5	52·1	2·38	1·88
S.D., M.I., or C.I. ..	87·8	60·6	3·20	2·18
Any "hard" end-point ..	96·7	66·1	3·52	2·38
Fatal atherosclerotic events ..	70·8	48·3	2·58	1·74

subjects affected per 100 man-years. Incidence rates were also calculated for major end-points in combination.

As indicated in table I, at any of the three levels of cigarette consumption examined, the incidence of clinical events attributable to atherosclerosis was lower in experimental subjects than in individuals on the control diet. Thus when cigarette consumption is the same, the effect of the experimental diet persists.

Although table I makes it clear that there was a dietary effect, whatever the inequalities of the smoking distribution, it is also desirable to determine whether the surplus of heavy smokers in the control group accounted, *in part*, for the more favourable experience of the experimental group. Toward this end, we have developed estimates of "smoking-adjusted" incidence rates—that is, estimates of the outcome which would have resulted if the subjects of each smoking stratum had been allocated in equal numbers to the control and experimental groups. This was done by multiplying the number of subjects affected in a given cigarette-smoking stratum of the control group by $(x+c)/2c$, in which c = number of control subjects in the stratum and x = number of experimental subjects in the stratum; and by making a corresponding calculation for the experimental group. Resulting figures for all strata were totalled. Figures for total man-years at risk were similarly adjusted before calculating the adjusted incidence-rates. The objective of the calculation is to estimate the answer to this question: if a given stratum of a control group contains $1/2(c+x)$ subjects, whose mean experience is similar to that of the c subjects actually allocated to that subgroup; and if a corresponding experimental subgroup likewise contains $1/2(c+x)$ subjects, with mean experience comparable to that of the x subjects actually observed; and if this is true for all smoking strata, then what is the predicted outcome of such a trial? The resulting estimates, given in table II, are nearly identical to the figures actually observed (bottom of table I), the surplus of heavy smokers in the control group having been fully offset by an even larger surplus of moderate smokers (10–20 cigarettes per day) in the experimental group. We conclude, therefore, that the uneven distribution of cigarette-smoking habits had no net effect whatsoever on the outcome of the trial.

Returning to table I, the outcome in the control group reveals the well-known correlation between cigarette smoking and incidence of atherosclerotic complications. The smoking effect is not apparent, however, in the group on experimental diet; indeed, the experience of heavy-smoking experimental subjects was no worse than that of light-smoking and non-smoking subjects on either diet. Whether this is a true interaction between a dietary effect and smoking habits is difficult to judge with confidence on the basis of these observations. A true interaction of this nature, if confirmed by future work, would have important practical and theoretical implications. However, Leren's secondary-prevention trial[2] did not show evidence of interaction between the smoking effect and the diet effect. The reports of other dietary trials have not, to our knowledge, dealt with this question.

2. Leren, P. *Acta med. scand.* 1966, suppl. no. 466.

In referring to a "rebound" in serum-cholesterol level on resumption of normal diet by experimental subjects, your article conveys a disturbing misinterpretation of our observations. As indicated in fig. 20 of our report, we tested this question by selecting the 10 experimental subjects and the 11 control subjects who had had the best and most prolonged adherence. During the 8 months before termination of the experimental diet, these two subgroups had nearly identical mean serum-cholesterol concentrations. This must be attributed to chance, since the larger groups from which the sub-samples were drawn displayed lower mean levels among the experimental subjects than among the controls (see fig. 5 of our report). On resumption of the regular diet, the experimental subgroup displayed a prompt serum-cholesterol rise comparable in magnitude to the fall seen at the start of the study. Their levels were now higher than those of the control subgroup. This was surely not a "rebound" phenomenon, but rather an expression of the fact that non-dietary influences had set serum-cholesterol levels higher in these 10 experimental subjects than in the 11 men with whom they were compared.

Wadsworth Veterans Administration Hospital and U.C.L.A. School of Medicine, Los Angeles, California.

SEYMOUR DAYTON
MORTON LEE PEARCE.

TABLE 5.—*Coronary heart disease morbidity as related to smoking—angina pectoris—prospective studies*

(Risk ratios—actual number of CHD manifestations shown in parentheses)[1]

(SM = Smokers NS = Nonsmokers)

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of incidents	Cigarettes/day	Cigars and pipes	Age variation	Comments
Doyle et al., 1964, U.S.A. (56).	2,282 males, Framingham, 30-62 years of age. 1,913 males, Albany, 39-55 years of age.	Detailed medical examination and follow-up.	10 8	81	NS .....1.00(30) All .....1.09(51) <20 .....1.17(15) 20 .....0.59(18) >20 .....1.18(18)			NS include ex-smokers and pipe and cigar smokers.
Jenkins et al., 1968, U.S.A. (60).	3,182 males aged 39-59 at entry.	Initial medical examination and follow-up by repeat examination.	4½	28	NS .....1.00 (8) All current cigarettes .....1.44(16) >16 .....1.63(14)			NS include former pipe and cigar smokers.
Kannel et al., U.S.A. (94).	5,127 males and females years of age 30-59	Medical examination and follow-up.	12	107	*Males* NS .....1.00(16) Heavy SM, >20 cigarettes .....2.04(17) *Females* NS .....1.00(55) Cigarette SM .....0.65(16)			
Shapiro et al., 1969, U.S.A. (172).	110,000 male and female enrollees of New York City HIP 35-64 years of age.	Baseline medical interview and examination and regular follow-up.	3	Total Unspecified	*Males* *Females* NS .....1.00 1.00 Current cigarettes †1.91 1.20 <40 .....1.51 } 1.20 >40 .....4.86 }	*Males* NS...1.00 SM...†1.71	*Males* *Females* *35–44 45–64 65–64* NS .....1.00 1.00 1.00 Current cigarettes ..3.40 1.67 2.06 <40 .....2.35 1.40 1.54 >40 .....10.15 2.65 6.15 *Females* NS .....1.00 1.00 1.00 Current cigarettes ..1.56 1.67 0.97 <40 .....1.67 1.63 1.04 >40 ..... — 4.12 —	†(p<0.01) †(p<0.05) NS include ex-smokers.

[1] Unless otherwise specified, disparities between the total number of manifestations and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

Numerous epidemiological studies have indicated that cigarette smokers have increased mortality ratios for CHD; that is, cigarette smokers show significantly increased death rates compared with nonsmokers (table 2). The risk incurred by cigarette smoking increases with increasing dosage and, as measured by mortality ratios, is more marked for men in the younger age groups, under age 60, although the absolute increment in death rates experienced by smokers over that of nonsmokers continues to increase with increasing age. Table 2 lists the mortality ratios found in the major studies. Certain of these studies, including those at Framingham, Massachusetts, the Health Insurance Plan of New York City (HIP), and at Tecumseh, Michigan, have analyzed morbidity as well as mortality from CHD and have indicated that the risk of developing fatal and nonfatal CHD is greater among cigarette smokers than among nonsmokers (tables 3 and 4). Conflicting evidence has been published concerning the relationship of cigarette smoking and the incidence of angina pectoris. While some

studies have shown an increased risk of this manifestation among smokers, others have not (see table 5).

From these longitudinal studies, it has become increasingly clear that cigarette smoking is one of several risk factors for CHD and that it exerts both an independent effect and an effect in conjunction with the other risk factors. The basic concept may be expressed as follows: The more risk factors a given individual has, the greater the chance of his developing CHD. The importance of the constellation of coronary risk factors which include cigarette smoking, high blood pressure, and high serum cholesterol in predicting the risk for CHD is illustrated in figures 1 through 3. Other risk factors are included in certain of these figures and are discussed below.

Knowledge of the effects of cigarette smoke on the cardiovascular system has developed concurrently with the knowledge derived from the epidemiological studies. Nicotine, as well as cigarette smoke, has been shown to increase heart rate, stroke volume, and blood pressure, all most probably secondary to the promotion of catecholamine release from the adrenal gland and other chromaffin tissue. This release of catecholamines is also considered to be the cause of the rise in serum free fatty acids observed upon the inhalation of cigarette smoke. Studies concerning the effect of nicotine on cardiac rhythm have also suggested that smoking might contribute to sudden death from ventricular fibrillation.

In addition, research efforts have also been directed toward the effects of smoking on blood clotting and thrombosis; since many cases of sudden death and myocardial infarction are associated with thrombosis in a diseased coronary artery branch. Cigarette smoking may be associated with increased platelet aggregation *in vitro* and thus might play a role in the development of such thrombi or platelet plugs *in vivo*.

Other mechanisms have been investigated. Because cigarette smoking has been shown in some studies to be related to the prevalence of angina pectoris as well as to the incidence of myocardial infarction, it has been suggested that smoking enhances the development of atherosclerotic lesions. Autopsy and experimental studies have shown that cigarette smoking plays a role in atherogenesis. The administration of nicotine has been observed to increase the severity of cholesterol-induced atherosclerotic lesions in experimental animals. Attention is presently being given to carbon monoxide, which is present in cigarette smoke in such concentrations as to cause carboxyhemoglobin concentrations in the blood of smokers as high as 10 percent. Based on research in animals, it is reasonable to conclude that the atherosclerotic process may be enhanced, in part, by the relative arterial hypoxemia in cigarette smokers caused by the increased carboxyhemoglobin level.

With respect to the acute event of myocardial infarction, attention has been focused on the role of nicotine. Nicotine stimulates the myocardium, increasing its oxygen demand. Other experiments have demonstrated that in the face of diminished coronary flow (due to partial occlusion from severe atherosclerosis in man or to partial mechanical obstruction in the animal), nicotine does not lead to an increase in coronary blood flow as seen in the normal individual. These effects exaggerate the oxygen deficit when the supply of oxygen has already been decreased by the presence of carboxyhemoglobin. Thus, a marked imbalance between oxygen demand (which has been increased) and oxygen supply (which has been decreased) is created by the inhalation of CO and nicotine. This imbalance may contribute to acute coronary insufficiency and myocardial infarction.

EPIDEMIOLOGICAL STUDIES

Numerous epidemiological studies, both retrospective and prospective, have been carried out in various countries in order to identify the risk factors associated with the development of coronary heart disease (CHD). Many of these studies have included smoking as one of the variables investigated. Tables 2 to 4 present the major findings.

CORONARY HEART DISEASE MORTALITY

Table 2 lists the various prospective studies concerning the relation of CHD mortality and smoking. These studies demonstrate the dose-related effect of cigarette smoking on the risk of developing CHD. For example, the Dorn Study of U.S. Veterans as reported by Kahn (*93*) reveals progressively increasing mortality ratios, from 1.39 for those smoking 1 to 9 cigarettes per day to 2.90 for those smoking more than 39 cigarettes per day. Although the data are not detailed in the accompanying tables, several of these studies have also shown that increased rates of CHD mortality are associated with increased cigarette dosage, as measured by the degree of inhalation and the age at which smoking began. Although not as striking, the data for females reveal the same trends.

In most studies, the smokers' increased risk of dying from CHD appears to be limited mainly to those who smoke cigarettes. Some studies that have investigated other forms of smoking have shown much smaller increases in risk for pipe and cigar smokers when compared to nonsmokers. However, the recent study by Shapiro, et al. (*172*) of a large population enrolled in the Health Insurance Plan (HIP) of New York City showed a significantly increased risk for the development of myocardial infarction and rapidly fatal myocardial infarction for a group consisting of both pipe and cigar smokers.

Table 3 details the findings of the American Heart Association Pooling Project on sudden death. The Pooling Project, a national cooperative project of the AHA Council on Epidemiology, is described in table 1 (*55*). Cigarette smokers in the 30 to 59 year age group incurred a risk of sudden death from CHD substantially greater than that of nonsmokers. Pipe and cigar smokers were observed to show a risk slightly greater than that of nonsmokers (table 3).

The relative risk of CHD mortality is greatest among cigarette smokers (as well as among those with other risk factors) in the younger age groups and decreases among the elderly. In table 2, Hammond and Horn found that for those smoking more than one pack per day, the risk is 2.51 in the 50 to 54 year age group and 1.56 in the 65 to 69 year age group. Although the relative risk for CHD among smokers decreases in the older age groups, the actual number of excess deaths among smokers continues to climb since the differences in death rates between smokers and nonsmokers continue to rise.

(93) KAHN, H. A. The Dorn study of smoking and mortality among U.S. veterans: report on 8½ years of observation. IN: Haenszel, W. (Editor). Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph No. 19, January 1966, pp. 1-125.

TABLE 19.—*Autopsy studies of atherosclerosis (cont.)*

(Figures in parentheses are number of individuals in that smoking category)*
(SM = smokers NS = nonsmokers)

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Conclusions	Comments
[illegible] et al., 1958, Chile (*888*).	1,169 males and 290 females who died violently in 1951-1954. Smoking information available only on 560 males.	Interview with relatives.	The results concerning internal fibrous streaks and fatty plaques in the left anterior descending coronary artery are reported in graphic form only. An examination of this data indicates that the moderate and heavy smokers appeared to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance.	The authors conclude that: "No relationship between atherosclerotic lesions and the use of tobacco was discernible."	
Group et al., 1969, U.S.A. (*888*).	747 males 25-64 years of age autopsied between 1953-1968 at Charity Hospital in New Orleans.	Interview with next of kin within 2 weeks of death.	*Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).* White: 25-34: 9 (14); 35-44: 11 (13); 45-54: 20 (6); 55-64: 33 (7). NS: 3 (6); 1-24 cigarettes/day: 9 (14); 25+ cigarettes/day: 12 (10). Negro: 25-34: 6 (14); 35-44: 8 (8); 45-54: 16 (13); 55-64: 17 (14). NS: 6 (14); 1-24 cigarettes/day: 3 (55); 25+ cigarettes/day: 17 (10).	The authors conclude that: "Atherosclerotic involvement of aorta and coronary arteries is greatest in heavy smokers and least in nonsmokers."	This report concerns only ages 25-64. No data on statistical significance provided.

*Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

Epidemiological Studies Criticized by Seltzer. The appraisal of the Royal College of Physician's Report by Seltzer (Lancet 1: 243-248, 1972) applies to the 1971 document. This was in turn followed by:

1. A letter from Fletcher (Lancet 12 February, 1972).
2. A letter from Sterling (Lancet 29 April, 1972).
3. A letter from Seltzer (Lancet 11 March, 1972).
4. A letter from Burch (Lancet 10 June, 1972).
5. A letter from Fletcher (Lancet 1 July, 1972), and finally
6. A letter from Doll (Lancet 15 July, 1972).

Occasional Survey

A CRITICAL APPRAISAL OF THE ROYAL COLLEGE OF PHYSICIANS' REPORT ON SMOKING AND HEALTH

CARL C. SELTZER

Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, U.S.A.

Summary The claims in the Royal College of Physicians' report *Smoking and Health Now* are examined with reference to certain secular changes in mortality for British doctors as compared with those for the general population. The data as presented are found to exhibit geographical and populational restrictions, age restrictions, and unexpected changes in classification of diseases; they also omit a crucial time period and assume certain unverified trends in smoking habits. The statements and claims of the Royal College of Physicians are not supported by the re-examination of certain data included in the report, and by an analysis of pertinent data that were omitted. The appraisal of the full data illustrates the hazards of drawing firm conclusions from secular changes in death-rates, and raises doubts that the Royal College of Physicians' report contains the "strongest evidence there is of the value of giving up cigarettes".

INTRODUCTION

IN 1971 the Royal College of Physicians (R.C.P.) issued a report entitled *Smoking and Health Now*.[1] A table in that report contained secular comparisons for the death-rates during 1953–57 and 1962–65 of two groups of men at ages 35–64. One group was taken from R. Doll and A. B. Hill's sample of British doctors; the other group was assembled from the Registrar General's data for England and Wales. According to the R.C.P. report, the contrasted data constitute "the strongest evidence there is of the value of giving up cigarettes".

The interpretation of secular changes in mortality is a difficult statistical procedure. As Bradford Hill has stated, "In making comparisons between death-rates from different causes at different times . . . it must be realised that one is dealing with material which is, in Raymond Pearl's words, 'fundamentally of a dubious character'".[2] Secular changes in these rates may be affected by vagaries of death-certificate reporting, such as accuracy of diagnosis, faulty certifications of death, and trends in reporting; and also by influences related to sex, race, socioeconomic status, geography, and occupation. The uncertain effects of these features are difficult to exclude when a specific exogenous factor is held responsible for the observed secular changes.

Because the comparison of secular death-rates is often an important technique in epidemiological analysis, and because the results of such a comparison have been made a central issue in the R.C.P. report, the validity of the statistical procedures has been appraised here.

CLAIMS OF THE R.C.P.

The R.C.P. drew its conclusions mainly from data in table 2.3 of its report (reproduced here in table 1), and stated that:

(1) The death-rate of British doctors declined more than that of the general population in the interval between the time periods 1953–57 and 1962–65.

(2) In the category "major diseases related to cigarette smoking", the death-rates declined in British doctors but increased in the general population.

(3) In the category "all unrelated causes", the death-rates declined equally in British doctors and in the general population.

From data elsewhere in the report, the R.C.P. also stated that British doctors' cigarette smoking declined by about 50% between 1951 and 1965, but "there was little corresponding change in the smoking habits of the general population during the same period".

The associated secular changes in death-rates and

TABLE I—CHANGES IN DEATH-RATES PER 100,000, STANDARDISED FOR AGE IN DOCTORS AND IN ALL MEN AGED 35–64 IN ENGLAND AND WALES 1953–1957 AND 1962–1965 (REPRODUCED FROM R.C.P. TABLE 2.3)

Cause of death	Male doctors			All men in England and Wales		
	Period		% Change	Period		% Change
	1953–57	1962–65		1953–57	1962–65	
Coronary heart-disease	294	277	−6	219	290	+32
Other cardiovascular diseases	167	157	−6	185	152	−18
All cardiovascular diseases	461	434	−6	404	442	+ 9
Cancer of the lung	60	37	−38	113	120	+ 6
Chronic bronchitis	18	14	−22	74	71	− 4
Major diseases related to cigarette smoking	539	485	−10	591	633	+ 7
Other cancers*	130	99	−24	152	145	− 5
Other causes*	184	163	−11	250	188	−25
All unrelated causes	314	262	−17	402	332	−17
All causes	853	747	−12	993	966	− 3

* These include a small number of deaths from cancers of mouth, throat, and œsophagus, from tuberculosis, from cirrhosis of the liver, and from peptic ulcer, which are related to cigarette smoking but make only a small contribution to the excess deaths of cigarette smokers.

in smoking were interpreted by the R.C.P. as follows. As cigarette smoking declined more for British doctors than for the general population, the death-rate between the two time-periods declined more for the doctors than for the general population. Furthermore, although the British doctors and the general population had similar changes in death-rates for diseases "unrelated" to cigarette smoking, the death-rates for the "major diseases related to cigarette smoking" declined for the doctors but rose for the general population. From these associations the R.C.P. concluded that "the benefit that British doctors have won at the peak of their professional careers provides the strongest evidence there is of the value of giving up cigarettes".

UNCERTAINTIES IN R.C.P. DATA

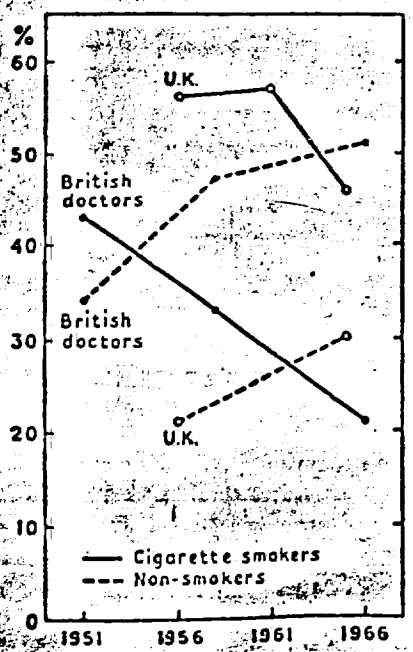
An examination of table I and the R.C.P. statements reveals several uncertainties and inconsistencies.

Data about Cigarette Smoking

According to the R.C.P. report, cigarette smoking between 1951 and 1965 declined among British doctors by about half (from 43% to 21%), and the proportion of non-smokers (including ex-smokers) rose from 34% to 51%. During this period, there was "a striking contrast between the smoking habits of doctors and those of other men [in the general population] over the age of 35 . . . [since] there was little corresponding change in the smoking habits of the general population during the same period".

The R.C.P. states that it obtained its data about the smoking habits of British doctors from the Doll and Hill 1964 study [3] and from Doll and M. C. Pike by personal communication. The R.C.P. source of its comments on the smoking habits of the men from the general population is clear for 1965 but not for the immediately prior periods. The figures for the smoking habits of United Kingdom men in 1965 were those published by the Tobacco Research Council (T.R.C.).[4]

The figure indicates the changes in the smoking habits of British doctors and United Kingdom men of the same ages between 1951 and 1966. For the sake of clarity, forms of smoking other than non-smoking and cigarette smoking have been omitted. (Following the procedures of the R.C.P., non-smokers consist of never-smokers and ex-smokers, while cigarette smokers refer to cigarette smokers only.) The data with regard to British doctors are those presented by the R.C.P. (in its fig. 1.4); the U.K. data for 1965 are those derived by the R.C.P. from T.R.C. data [4]; U.K. figures for 1961 have been derived by me from the same source,[4] and those for 1956 have been obtained from an earlier research paper of the Tobacco Research Council.[5] Earlier U.K. data (in the same form) for 1951–55 are not available from the Tobacco Research Council survey.



Changes in smoking habits of British doctors and men in U.K. aged 35 and over.

According to T.R.C. data, between 1951 and 1956 cigarette consumption per adult male in the U.K. increased by only 4%. This figure refers to cigarette consumption, not proportion of cigarette smokers; nevertheless, it seems reasonable to conclude that the proportion of cigarette smokers among U.K. men did not change strikingly between 1951 and 1956. After 1956, however, the proportion of non-smokers in the U.K. over the age of 35 increased by 15% (see figure), and the corresponding rise for British doctors was 19%. Cigarette smokers constituted 56% of the U.K. men in 1956 and 57% in 1961, but only 46% in 1965, a change of 19%. From 1961 to 1965, cigarette smoking among British doctors dropped by 19%. These findings receive further confirmation from R.C.P. fig. 1.1, which shows a drop in cigarette consumption among men in the U.K. population since 1960.

These data thus support the R.C.P.'s contention that the proportion of cigarette-smoking British doctors fell between 1951 and 1965, but they do not support the statement about "little corresponding change" in the general population. From 1956 to 1965, the non-smokers in the general population increased at a rate similar to that shown by British doctors. From 1961 to 1965 the percentage of cigarette smokers decreased at about the same rate in both the general population and the doctors.

Changes in Classification of Disease

Another interesting feature of the R.C.P. table is the classification of disease, which was done by the R.C.P. in a manner different from that of Doll and Hill. In Doll and Hill's published studies of British doctors in 1964 and 1966,[3,6] the diseases regarded as "related" to cigarette smoking were cancer of the lung and upper respiratory and digestive tracts, chronic bronchitis, coronary heart-disease, peptic ulcer, cirrhosis of the liver, and pulmonary tuberculosis. Under "unrelated causes", Doll and Hill included other cancers, other respiratory disease, cerebrovascular disease, other cardiovascular disease, violence, and other causes.

In the R.C.P. tabulation, many of Doll and Hill's "unrelated diseases" were transferred to the category of "related" diseases; thus among "major diseases related to cigarette smoking" are rheumatic fever, rheumatic pericarditis, endocarditis, and myocarditis, diseases of the mitral, aortic, and tricuspid valves, acute and subacute bacterial endocarditis, gangrene, varicose veins, and hæmorrhoids. These and other diseases listed by the R.C.P. under "other cardiovascular diseases" comprise numbers 400–468 (all diseases of the circulatory system, less 420) and 330–334 (vascular lesions affecting the central nervous system) of the International Statistical Classification of Diseases, Injuries and Causes of Death.[7]

No explanation is provided for these changes in the Doll/Hill classification, although the R.C.P. report relied so heavily on other aspects of the Doll/Hill data. Explanations were, however, provided for certain changes from "related" diseases to "unrelated" diseases.

Geographic Restrictions

The R.C.P. compared death-rates for British doctors and for all men in England and Wales. The Doll/Hill sample of British doctors,[3] however, was drawn from the U.K. (Scotland and Northern Ireland, as well as England and Wales). The contrasted populations are thus geographically different: a more suitable comparison for the British doctors would be with all men in the United Kingdom, since the male death-rates of the U.K. may differ from those of only England and Wales.

Population Restrictions

Doctors are not typical of all men in England and Wales. They differ in race, social and economic status, "life style", education, and other characteristics that are themselves related to rates of disease and mortality, and that may affect trends in death-rates for the contrasted populations.

Age Restrictions

The R.C.P. data are restricted to men ages 35 to 64, although the data for all adult ages would ordinarily extend from ages 35 to 84. Since the R.C.P. statements are not confined to conclusions about the health of cigarette smokers only at ages 35–64, the absence of data for all adult ages would be a significant limitation on the R.C.P. conclusions.

Intermediate Time Period

The R.C.P. compared death-rates for the periods 1953–57 and 1962–65, omitting 1958–61. When two separated periods in time are compared without regard to the intervening period, any conclusions about a trend are tenuous, because the intermediate data may alter any trend found between the two extremes of time.

AUGMENTATION OF R.C.P. DATA

Apart from the uncertainties in the sampling of doctors, the unexplained changes in classification of disease, and the inaccurate description of smoking habits for the general population, the R.C.P. report did not consider the omissions just cited in geography, age, and time periods. Since the missing data might help clarify some of the issues, a reanalysis of the R.C.P. contentions seemed desirable, with the data expanded to include geographic, age, and temporal information that had been omitted in the R.C.P. report. The additional details for these features of the general population of the U.K. were obtained from the Registrar General's reports.[8] The corresponding details about the British doctors were obtained from the latest Doll and Pike report.[9]

Missing Time Period

For the same ages and geography used in the R.C.P. report, the data of the missing time interval are shown here in table II. This table indicates the annual age-standardised rates per 100,000 men aged 35–64, for British doctors and all men in England and Wales during the three successive periods 1953–57, 1958–61, and 1962–65. In table III the "absolute" values shown in table II are converted into percentage changes in death-rates during the three time periods. The figures in tables II and III show the following results that are pertinent to the R.C.P. statement.

The claim that total death-rates of doctors declined more than those of the general population.—As shown

TABLE III—% CHANGES IN AGE-STANDARDISED DEATH-RATES PER 100,000 FOR BRITISH DOCTORS AND ALL MEN IN ENGLAND AND WALES AGED 35–64*

Cause of death	British doctors		All men in England and Wales	
	From 1953–57 to 1958–61	From 1958–61 to 1962–65	From 1953–57 to 1958–61	From 1958–61 to 1962–65
Coronary heart-disease	− 7	+ 1	+15	+15
Other cardiovascular diseases	+18	−20	−10	− 9
All cardiovascular diseases	+ 2	− 8	+ 4	+ 5
Cancer of the lung	− 7	−34	+ 5	+ 1
Chronic bronchitis	−33	+17	− 1	− 3
Major diseases related to cigarette smoking	0	−10	+ 3	+ 4
Other cancers	− 6	−20	− 2	− 3
Other causes	+ 5	−16	−16	−11
All unrelated causes	+ 1	−17	−10	− 8
All causes	0	−13	− 2	− 1

* % changes are used in this form to conform with R.C.P. practice.

TABLE II—AGE-STANDARDISED ANNUAL DEATH-RATES PER 100,000 MEN, AGES 35 TO 64*
(ADAPTED TO DISEASE CLASSIFICATIONS OF R.C.P. TABLE 2.3)

Cause of death	British doctors			All men in England and Wales		
	1953–57	1958–61	1962–65	1953–57	1958–61	1962–65
Coronary heart-disease	294	273	277	219	252	290
Other cardiovascular diseases	167	197	157	185	167	152
All cardiovascular diseases	461	470	434	404	419	442
Cancer of the lung	60	56	37	113	119	120
Chronic bronchitis	18	12	14	74	73	71
Major diseases related to cigarette smoking	539	538	485	591	611	633
Other cancers	130	123	99	152	149	145
Other causes	184	193	163	250	211	188
All unrelated causes	314	316	262	402	360	332
All causes	853	854	747	993	971	966

* The data for the first and last time periods are taken from the R.C.P. report. The data for the middle time periods were derived from the Doll and Pike report.[9] For British doctors, the years run from Nov. 1 to Oct. 31. To maintain consistency with R.C.P. table 2.3, we have followed the R.C.P. labelling of the period years.

in table III, the reduction in cigarette smoking among British doctors between 1953–57 and 1958–61 was not accompanied by any change in overall death-rate. During the same interval the death-rate for all men in England and Wales fell by 2%. Between 1958–61 and 1962–65, the total death-rates of British doctors fell more than those of the general population, although cigarette smoking from 1951 to 1965 declined at least as fast in terms of percentage among the general population than in British doctors. From 1958–61 to 1962–65, the reduction in total death-rates was 1% in the general population and 13% in the British doctors. Thus, when the three time periods are considered successively, the total death-rates of British doctors are not found to have declined consistently more than the general population.

The claim that death-rates for "all unrelated causes" declined equally in British doctors and in the general population.—This assertion is not supported by the data in tables II and III. From 1953–57 to 1958–61, the death-rates for "unrelated causes" among British doctors rose by 1% while those of the general population fell by 10%. From 1958–61 to 1962–65, the death-rates for these "unrelated causes" decreased by 17% in British doctors and by 8% in the general population.

The claim that death-rates for "major diseases related to cigarette smoking" declined in the British doctors but increased in the general population.—From 1953–57 to 1958–61, there was no drop in the death-rates of British doctors for "major diseases related to cigarette smoking". The rates were essentially the same: 539 and 538 per 100,000 men, respectively. For the same category of diseases over the same interval, the death-rates increased by 3% in all men in England and Wales. In the second interval, however, the R.C.P. claim is confirmed. The death-rates declined (−10%) in British doctors and rose (+4%) in the general population. The general population's increase in death-rates between 1958–61 and 1962–65 occurred, however, despite the concomitant reduction in cigarette smokers of this population between 1961 and 1965.

Inconsistencies in patterns of specific diseases.—Tables II and III contain several inconsistencies in the patterns of specific diseases—especially in the data of British doctors for changes in death-rates between the first interval (1953–57 to 1958–61) and the second interval (1958–61 to 1962–65). For example, in British doctors, the death-rate for coronary heart-disease declined in the first interval and rose in the second interval; the death-rates for "other cardiovascular diseases" and for "all cardiovascular diseases" rose substantially in the first interval and then fell substantially in the second. The rate for chronic bronchitis fell by 33% and then rose by 17%. For the categories of "all causes", "major diseases related to cigarette smoking", and "unrelated causes", the British doctors had almost no changes in the death-rates in the first interval, followed by notable decreases in the second interval. These inconsistencies occurred despite the almost constant rate of decline of cigarette smoking among British doctors from 1951 to 1966. For the general population of England and Wales, on the other hand, the trends of death-rates were strikingly consistent for the specific disease categories in both the first and second intervals despite the inconstant cigarette smoking patterns in this population. As previously noted, the proportion of cigarette smokers in the general population changed little between 1956 and 1961, but then dropped sharply from 1961 to 1965.

Missing geography.—The death-rates for all men in the United Kingdom ages 35–64 (in contrast to all men in England and Wales) have been derived for the missing period 1958–61 from the Registrar General's reports (table IV). These data permit a comparison of the death-rate changes for the two intervals (from 1953–57 to 1958–61 and from 1958–61 to 1962–65) in the men of the United Kingdom—a more suitable comparison for the sample of British doctors. In the data for U.K. men, the death-rates for all causes fell in the first interval (while smoking habits were essentially unchanged), and stayed virtually the same in the second interval (while smoking decreased). The death-rates for "related" diseases rose in the first period and continued to rise in the second. For "unrelated" diseases, the death-rate of U.K. men fell more in the first interval (−12%) than in the second (−8%). Thus, when the missing time period and missing geography are taken into consideration for ages 35–64, the claims of the R.C.P. are not substantiated. The discrepancies are most notable for the events of the first interval.

TABLE IV—AGE-STANDARDISED DEATH-RATES PER 100,000 IN BRITISH DOCTORS AND IN MEN OF UNITED KINGDOM

Deaths from	British doctors			United Kingdom		
	1953–57	1958–61	1962–65	1953–57	1958–61	1962–65
Ages 35–64:						
Related causes	539	538	455	586	614	639
Unrelated causes	314	316	262	425	375	346
All causes	853	854	747	1011	989	985
Ages 35–84:						
Related causes	1180	1231	1202	1401	1435	1473
Unrelated causes	560	570	528	817	762	719
All causes	1740	1801	1730	2218	2197	2192

Missing Ages

In this section, the data are expanded to include the missing ages (35–84) as well as the missing time period (1958–61).

Table V shows the death-rates of the British doctors and all men in England and Wales, ages 35–84, for the three successive time periods 1953–57, 1958–61, and 1962–65. The percentage changes over the two time intervals are presented in table VI. The figures in these tables show the following results that are pertinent to the R.C.P. statements.

Claim that total death-rates of doctors decline more than those of the general population.—In the age-groups 35–84, for the time periods considered by the R.C.P., the death-rates of British doctors did not consistently decline more than those of the general population. Between the two external time periods (1953–57 and 1962–65) the total death-rate of British doctors fell

TABLE V—AGE-STANDARDISED ANNUAL DEATH-RATES PER 100,000 MEN, AGES 35–84*
(ADAPTED TO DISEASE CLASSIFICATIONS OF R.C.P. TABLE 2.3)

Cause of death	British doctors			All men in England and Wales		
	1953–57	1958–61	1962–65	1953–57	1958–61	1962–65
Coronary heart-disease	519	564	559	425	491	564
Other cardiovascular diseases	507	533	506	682	603	541
All cardiovascular diseases	1026	1097	1065	1107	1094	1105
Cancer of the lung	110	85	83	149	171	188
Chronic bronchitis	44	49	54	160	170	184
Major diseases related to cigarette smoking	1180	1231	1202	1416	1435	1477
Other cancers	253	236	224	307	301	294
Other causes	307	334	304	482	438	406
All unrelated causes	560	570	528	789	739	700
All causes	1740	1801	1730	2205	2174	2177

* British doctors' data derived from Doll and Pike.[4] For British doctors, the years run from Nov. 1 to Oct. 31. For reasons of consistency with R.C.P. table 2.3, we have followed the R.C.P. labelling of the period years.

by only 0·6% (1740 to 1730), as compared to a decline of 1·3% (2205 to 2177) in all men in England and Wales. When the additional age range and missing time periods are inspected, the death-rate for the British doctors is seen to have increased by 4% from 1953–57 to 1958–61, despite the concomitant decrease in cigarette smoking. Over the same interval the death-rates for the general population declined by 1%. From 1958–61 to 1962–65, British doctors' overall death-rate declined more than that of the general population, which showed essentially no change, despite the drop in cigarette smoking.

Claim that the death-rates for the category of "all unrelated causes" declined equally in British doctors and in the general population.—This claim is not supported by the data for ages 35–84. Between the external periods 1953–57 and 1962–65, the reduction in death-rates for "unrelated causes" in the general population (11%) was almost twice as great as the comparable decline in the British doctors (6%). When the data are examined for the effects of the missing time period, the R.C.P. contention is about right for the second time interval, but not for the first. In the first interval the death-rate for "unrelated causes" increased by 2% in the British doctors, in contrast to that of the general population, which showed a 6% drop.

Claim that the death-rates of "major diseases related to cigarette smoking" declined in British doctors but increased in the general population.—Again, this assertion is not fully supported by the data for ages 35–84. From the "outside" time periods, 1953–57 to 1962–65, the death-rates for "related" diseases increased in both populations, rising by 2% in British doctors and by 4% in all men in England and Wales. For the first "inside" interval, from 1953–57 to 1958–61, the data of ages 35–84 also do not support this R.C.P. contention. The death-rates for the classification "major diseases related to cigarette smoking" increased in both British doctors (4%) and in the general population (1%). In the second interval doctors' death-rates declined (2%) and the general population rates increased (3%). Thus, the apparent contradiction of a rising death-rate during a fall in smoking occurred in British doctors for the first interval and in the general population for the second.

TABLE VI—% CHANGES IN AGE-STANDARDISED DEATH-RATES PER 100,000 FOR BRITISH DOCTORS AND ALL MEN IN ENGLAND AND WALES AGED 35–84.

Cause of death	British doctors		All men in England and Wales	
	From 1953–57 to 1958–61	From 1958–61 to 1962–65	From 1953–57 to 1958–61	From 1958–61 to 1962–65
Major diseases related to cigarette smoking	+4	−2	+1	+3
All unrelated causes	+2	−7	−6	−6
All causes	+4	−2	−1	0

Inconsistencies in patterns of specific diseases.—An additional inconsistency in the R.C.P. data is noted for coronary heart-disease. For ages 35–84, the death-rates from 1953–57 to 1962–65 in British doctors increased by 8% during a period of declining cigarette smoking. In addition, although the category of "other cardiovascular diseases" showed no change in British doctors aged 35–84 between the same two periods, the death-rates for the same diseases declined by 21% in all men in the general population of England and Wales. The death-rates for "all cardiovascular disease" increased by 4% in British doctors aged 35–84, in contrast to essentially no change for all men in England and Wales. Other inconsistencies occur in the patterns of specific diseases in the expanded age-and-time data. In British doctors, the death-rates for coronary heart-disease, for "other cardiovascular diseases", and "all cardiovascular disease" increased in the first interval and decreased in the second. Despite a constant decline in doctors' cigarette smoking, cancer of the lung decreased by 23% over the first interval and by only 2% in the second interval.

With respect to all men in England and Wales, the trends in death-rates for the specific diseases are quite consistent in both the first and second intervals, despite the inconstant changes in smoking habits in the general population.

Missing geography.—The bottom part of table IV summarises the expanded geographical data for the augmented age and time intervals. The lower half of this table shows the age-standardised death-rates per 100,000 men ages 35–84 for British doctors and for all men in the United Kingdom during the successive periods 1953–57, 1958–61, and 1962–65. The data show differences in the death-rates for the men in the United Kingdom as compared to corresponding results for the men in England and Wales shown in table V. The basic trend in the changes from one time period to the next for the United Kingdom men are not appreciably different from those found in the corresponding figures for England and Wales. Consequently, it seems reasonable to conclude that the omissions in age and time period, rather than geography, are responsible for any distortions or discrepancies in the claims of the R.C.P.

DISCUSSION

The statements and claims of the Royal College of Physicians, based on table 2.3 of the R.C.P. report, are not supported by a re-examination of certain data in the report and by analysis of data that were omitted.

One basic argument of the R.C.P. rests on the assertion that cigarette smoking fell in British doctors without a comparable decline in smoking in the general population. This assertion does not seem true for the period 1961 to 1965, when the per cent decrease of cigarette smokers was about the same in the general population as in the Doll/Hill sample of British doctors.

In addition, the omission of data for the age group 35–84 and for the middle time period (1958–61) has created an erroneous parallelism of falling death-rates and declining cigarette smoking in British doctors. When considered for ages 35–84 rather than 35–64, the death-rates of British doctors did not consistently decline, and for most diseases actually rose rather than fell for the two time periods considered by the R.C.P. When these two time periods are augmented by their middle period (1958–61) the doctors' death-rates showed many inconsistencies.

It might be argued that the benefits derived from stopping cigarette smoking take time to appear, and that the interval from 1953–57 to 1958–61 is too short to show any appreciable reduction in death-rates for certain causes of disease. However, table 25 in Doll and Hill's 1964 report on the British doctors [3] shows that in less than five years after smoking was stopped, the death-rate of former cigarette smokers had fallen by 25% from the level of continuing cigarette smokers (from 7·19 to 5·36 per 1000) for "related diseases" and by 34% for the "unrelated diseases" (from 9·43 to 6·26 per 1000). In interpreting these data, Doll and Hill concluded that "the fall in mortality with the stopping of smoking is a real effect as far as the 'related' diseases are concerned, while for the 'unrelated' diseases it is an artifact due to selection".

Regardless of the reasons for the decline, the mortality-rates of former cigarette smokers seem to decline "immediately" after smoking is given up. Such a decline, however, was not reflected in the mortality-rates for British doctors from the period 1953–57 to 1958–61. On the contrary, from 1953–57 to 1958–61, when the proportion of cigarette smokers dropped sharply, the death-rates of British doctors (ages 35 to 84) showed an increase of 4%, 2%, and 4%, respectively, for "related causes", "unrelated causes", and "all causes", and for ages 35–64 changes of 0%, +1%, and 0%.

A curious feature of Doll and Hill's 1964 report on British doctors is that the death-rates of former cigarette smokers (less than 5 years after stopping smoking) fell more for "unrelated causes" than for "related causes". This inconsistency is also found in R.C.P. table 2.3, where for British doctors the death-rates for "unrelated causes" fell by 17%, compared to a 10% fall for "major diseases related to cigarette smoking".

The absence of data for all adult ages in the R.C.P. report is significant but seems less serious than the omission of the data for the middle time period, 1958–61. Since a consideration of the middle-period data seems to alter the results so distinctly, the omission of this information is unfortunate.

This reappraisal of the full data provides strong support for Bradford Hill's injunction about the hazards of analysing secular changes in death rates. The reappraisal also raises major doubts about the Royal College of Physicians' conclusion that it has presented "the strongest evidence there is of the value of giving up cigarettes".

This study was supported in part by the Fund for Research and Teaching of the Department of Nutrition, Harvard School of Public Health.

REFERENCES

1. Smoking and Health Now: a report of the Royal College of Physicians. London, 1971.
2. Hill, A. B. Principles of Medical Statistics; p. 201. London, 1956.
3. Doll, R., Hill, A. B. *Br. med. J.* 1964, i, 1399, 1460.
4. Todd, G. F. (editor). Statistics of Smoking in the United Kingdom: Tobacco Research Council research paper no. 1. London, 1969.
5. Todd, G. F. (editor). Statistics of Smoking in the United Kingdom: Tobacco Research Council research paper no. 1. London, 1957.
6. Doll, R., Hill, A. B. *Natn. Cancer Inst. Monogr.* 1966, no. 19, p. 205.
7. Registrar General's statistical reviews of England and Wales for the years 1953 and 1958. H.M. Stationery Office.
8. Registrar General's Statistical Review of England and Wales for the years 1953–62; Annual Report of the Registrar General for Scotland, 1953–62; Annual Report of the Registrar General for Northern Ireland, 1953–62.
9. Doll, R., Pike, M. C. *Jl R. Coll. Physns, Lond.* 1972, 6, 216.

SMOKING AND HEALTH

SIR,—Dr. Seltzer's article (Jan. 29, p. 243) on the Royal College of Physicians' report on smoking and health is in fact concerned only with one table in the report and the conclusions derived from it that stopping smoking increases life expectation. With this he disagrees. The inadequacy of Dr. Seltzer's arguments are so well presented by your leading article and by Sir Richard Doll (Feb. 5, p. 322) that no more need be said about them, but one error should be corrected. He says that no reason was given for the classification of diseases related and unrelated to cigarette-smoking which was used in the table. If he had read the rest of the report he would have found the explanation in paragraph 6.11. There he would also have found a reference to independent evidence of a favourable trend in coronary deaths among doctors associated with their decline in cigarette-smoking, which he does not consider in his article.

C. M. FLETCHER,
Secretary,
Royal College of Physicians' Committee on Smoking and Health.

Department of Medicine,
Royal Postgraduate Medical School,
Hammersmith Hospital,
London W.12.

REPORT ON SMOKING AND HEALTH

SIR,—In your issue of Jan. 29 (p. 243) you published a paper by Dr. Carl C. Seltzer in which he examined some of the data on which the Royal College of Physicians based its conclusions concerning cigarette smoking and health. In an accompanying editorial (p. 238) you expressed considerable criticism of Dr. Seltzer's critique.

The editorial disputed Dr. Seltzer on one main point. The Royal College of Physicians had attached particular importance to the observation that between 1953 and 1965 the mortality in male British doctors, many of whom it was believed had stopped smoking, decreased more rapidly than in all men of the same age in England and Wales, among whom it was believed that smoking habits had remained relatively unchanged. Seltzer objected to the geographical, population, and age restrictions and unexpected changes in classification of disease in the data used by the Royal College, to the omission of crucial time periods, and to the assumption of unverified trends in smoking habits. Seltzer found that, once all the data were included which he considered to be pertinent, differences in mortality trends between former smokers and non-smokers largely disappeared.

Dr. Seltzer's findings also were attacked by Sir Richard Doll (Feb. 5, p. 322), who pointed out that pattern of change in mortality with the length of time that smoking had been stopped varied with the nature of the disease, but that ". . . after smoking had been stopped for ten or more years the mortality from 'related causes' had fallen by 38% . . .".

Now I find it extremely curious that Seltzer's conclusions, disputed in that editorial, had been quietly conceded by others, foremost of whom is Doll. In an analysis of lung-cancer death-rates presented to the Royal Statistical Society—an analysis of the same data on which the R.C.P. has based its report—Doll says: "The impression has, therefore, been gained that the incidence of the disease falls when smoking is stopped. In fact, this is not necessarily so; and the published results are compatible with the decreasing incidence, the constant incidence, or one which rises steadily but less rapidly than in men who continue to smoke." And, on the same page: "The results are compatible with the hypothesis that damage produced by smoking is irreversible and that the risk remains practically the same as it was when smoking was stopped; the trend, however, is smooth and suggests that the risk may fall slightly at first and rise again slowly in keeping with the increase in risk in non-smokers."[4] Here Doll maintained for lung cancer precisely what Seltzer did for all mortality—namely, that when all pertinent time periods are considered, the change in mortality between non-smokers and those who cease smoking differs in no way. Doll used this assertion to support his claims that the damage done by smoking is irreversible. The Royal College (and Doll on other occasions) have given a different slant to the same data.

Your editorial criticised Seltzer also for disputing the belief that since 1960 smoking declined among British doctors but not in the general population. Here, again, we find that Doll, too, reported the disputed decline in cigarette consumption among men in the United Kingdom.[5] According to substantive evidence available for some time then, it would appear that Dr. Seltzer's critique was justified.

The issue of smoking and health calls forth emotional responses of which we all need to beware, since they tend to distort the scientific process. One example of what may happen is the way all parties have ignored the tenuous base of their numbers game. Doll's data on British physicians are based on a self-selected sample of physicians who voluntarily responded to questionaries. 30% of the physicians failed to respond to the original inquiry,[6] and the proportion of respondents has continuously decreased since then with each follow-up attempt. The danger of drawing conclusions from samples with high non-response rates has been generally recognised. Bradford Hill calls a non-response rate of 2 to 3% "satisfactorily small".[7] And, indeed, the characteristics of responding physicians are reported to be quite different from those of the general population.[8] As a result, any differences between observations on volunteering physicians and on census populations are difficult to interpret. In addition, estimates of smoking rates are uncertain in the extreme. Estimates of the smoking habits of the same population by use of similar methods may differ by more than a third for some age-groups.[9] From data with all these shortcomings, not much can be learned.

Department of Applied Mathematics
and Computer Science,
School of Engineering and Applied Science,
Washington University,
St. Louis, Missouri 63130. THEODOR D. STERLING.

SMOKING AND HEALTH

SIR,—Your editorial accompanying my article of Jan. 29 (p. 243) offered some apparent justification for the omission of data in the Royal College of Physicians' (R.C.P.) report on smoking and health [1] and raised a question about my own sources of data. I should like to comment on the points raised.

(1) The R.C.P. analysed data for ages 35–64. The analysis did not include data for ages 65–84 or the total results for ages 35–84. You imply that the missing data were not important, because of an allegedly lesser smoking effect in older age-groups. Nevertheless, your conclusions (and those in the R.C.P. report) referred to general effects of stopping smoking; not to any one age-group. Since the trends cited by the R.C.P. for ages 35–64 become reversed or distinctly muted when the data are examined for ages 35–84, this additional information warranted inclusion in the report. The extrapolation of the conclusion to all age-groups certainly seems inappropriate.

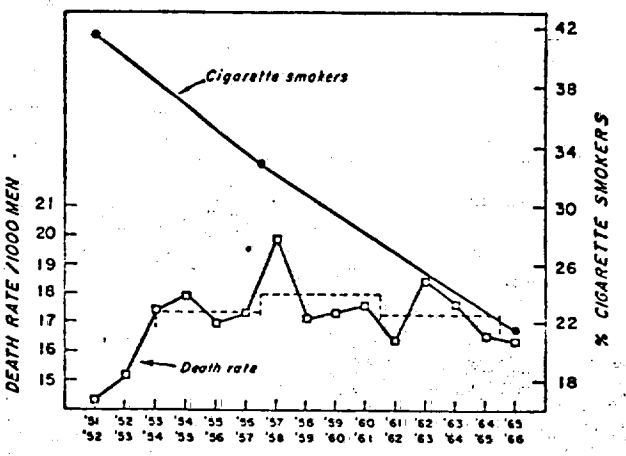
(2) The trends reported by R.C.P. were obtained by a comparison of data for 1953–57 and 1962–65. A straight line can always be drawn between two points, but the validity of the trend is enhanced if at least three points fit the line. The R.C.P. report did not include data for such a third point—the intermediate time period 1958–61. When data for the missing "middle point" are included many of the apparent trends vanish or are substantially altered. You justify the omission of this important middle time period by stating that the main effects of stopping smoking, although observed "surprisingly quickly", are seen more clearly 5–10 years later. If this statement is correct, the trends noted from the first to the intermediate time period should follow the same direction as the trends noted between the intermediate and later time period. For many of the cited diseases, however, the R.C.P. data do not confirm this expectation. In coronary heart-disease, for example, the downward trend at ages 35–64 from 1953–57 to 1958–61 is reversed to a slight upward trend from 1958–61 to 1962–65.

(3) The report's claims rest on the statement that during the cited time periods, cigarette smoking declined among British doctors but not in the general population. In my paper I pointed out the inaccuracy of this statement, and noted that from 1961 to 1965 the percentage of cigarette smokers decreased at about the same rate in men of both the medical and general populations. This same observation (of a decline in cigarette smokers after 1960) was made by Doll in his fig. 3 and text of a previous report [2]: "... the per caput consumption of cigarettes ... in men ... began to fall [after 1960]".

You question the source of my data about cigarette smoking. The data for the British doctors came from the R.C.P. report.[1] The data for the U.K. general population came from the same source [3] used by Doll.[2] To convert the original citations into the reported data, I used certain computations that were not published. The details of these computations for the years 1956, 1961, and 1965 are as follows:

Computations of 1956 cigarette smokers only figure of 56%.—Table 7 of the 1957 T.R.C. report [3] gives the % of men for 1956 ages 35–69 smoking packeted cigarettes only as 52·3%, hand-rolled only as 5·7%, hand-rolled and packeted cigarettes as 3·1%, making a total of 61·1%. The % of men ages 60+ smoking packeted cigarettes only is given as 33·3%, hand-rolled only as 6·7%, hand-rolled and packeted cigarettes as 1·7%, making a total of 41·7%. The U.K. adult male 1956 population was 7,473,000 for ages 35–59 and 3,020,000 for ages 60+. To compute % of cigarette smokers only for ages 35+ take 61·1% of 7,473,000 and add 41·7% of 3,020,000 and divide by total population 10,493,000 × 100 = 56%.

Computations of 1961 cigarette smokers only figure of 57%.—Table 12 of the 1969 T.R.C. report [4] gives the number of cigarette smokers only for men for 1961 ages 35+ as 7,120,000 and the total number of smokers for men ages 35+ as 9,220,000. Therefore, percentage of cigarette only smokers as a proportion of all smokers ages 35+ = 7,120,000/9,220,000 or 77%. Table 11a of the 1969 T.R.C. report gives the % of male non-smokers (including ex-smokers) ages 35–59 as 25% (base 1992) and for ages 60+ as 29% (base 789). Therefore, % non-smokers ages 35+ = 25 × 1992 + 29 × 789/2781 = 26%. Percentage of smokers ages 35+ is accordingly 74% (100 − 26). % of cigarette smokers only is 77% of 74%, or 57%.



Secular trends in death-rates and percentage cigarette smokers for British doctors ages 35 to 84 from 1951 to 1966 (standardised for age).

Death-rates taken from table 1 and percentage cigarette smokers from table 4 of Doll and Pike.[3] The dashed lines (semi-bar graphs) show average death-rate values for the periods 1953–57, 1957–61, and 1961–65 as given in table 2 of Doll and Pike.[3]

Computations of 1965 cigarette smokers only figure of 46%.—Table 12 of the 1969 T.R.C. report gives the number of cigarette smokers only for men for 1965 ages 35+ as 5,891,000 and the total number of men smokers ages 35+ as 8,877,000. Therefore, the % of cigarette only smokers as a proportion of all smokers ages 35+ = 5,891,000/8,877,000 or 66%. Table 11a of the T.R.C. report gives the % non-smokers (including ex-smokers) ages 35–59 as 29% (base 1618) and for ages 60+ as 31% (base 720). Therefore, % non-smokers ages 35+ = 29 × 1618 + 31 × 720/2338 = 30%. Percentage of smokers ages 35+ is accordingly 70% (100 − 30). % of cigarette smokers only is 66% of 70%, or 46%.

The results pertain only to the percentage of cigarette smokers, and data were not available for the years before 1956. For the crucial time period between 1961 and 1965 (not the earlier period, as asserted in your editorial), cigarette smoking declined in the general population, although the overall death-rate remained essentially the same. You did not comment on this crucial phenomenon, despite the doubt it raises for the claim that death-rate is reduced by stopping smoking.

Your statement that the "overall consumption of tobacco in the country as a whole has changed very little" is curious. The data to support this statement are attributed to a paper by Doll and Pike [5] and indicate that the average number of cigarettes smoked per day by all adult males in the U.K. was 11·0 for 1951, 11·5 for 1957, and 11·4 for 1966. However, you omit some important intermediate time periods. By computations from the same source [3] used by Doll and Pike, I have found that the comparable figures were 12·5 for 1961 and 11·4 for 1965, thus confirming that a decline in cigarette smoking occurred from 1961 to 1965. Since Doll had previously [2] acknowledged the reduction in the general population's cigarette smoking after 1960, you have placed Doll in the position of contradicting himself.

Your editorial attributed to the paper by Doll and Pike [5] figures of the average numbers of cigarettes smoked per day by doctors (ages 35–61) as 10·8, 8·3, and 5·5 for the years 1951, 1957, and 1966, respectively. But Doll and Pike's paper does not contain such data.

(4) A final point that can be noted in the recent Doll and Pike report [5] is the relationship between death-rate and a reduction in cigarette smoking among British doctors. From tables 1, 2, and 4 of that report, I constructed the accompanying figure. The years 1951–52 and 1952–53 are omitted because of Doll and Pike's suggestion [5] that the mortality-rates in those years are "obviously biased" by the way the cohort of British doctors was selected. The graph shows no correspondence between the death-rates among British doctors from 1953 to 1965, and their simultaneous downward trend in cigarette smoking.

These data from the Doll and Pike report provide perhaps the most vigorous refutation yet offered for the conclusion in your editorial and in the R.C.P. report that "changes in mortality among British doctors provide strong evidence that stopping smoking increases the expectation of life".

Department of Nutrition,
Harvard University School of Public Health,
Boston, Massachusetts, U.S.A. CARL C. SELTZER.

SMOKING AND HEALTH

SIR,—Are we to judge from their silence that Dr. Seltzer's critics have conceded his case (Jan. 29, p. 243, and March 11, p. 586)? Is cigarette-smoking non-lethal?

If the undoubted positive associations between cigarette smoking and death-rates from various diseases are not causal in origin, an alternative explanation is needed. According to Fisher,[1] such associations might arise from constitutional factors. That is to say, one or more of the genes that predispose to certain forms of smoking might be the same as, or linked with, genes that predispose to fatal disorders such as lung cancer. In principle, we can discriminate between causal and constitutional hypotheses by examining deaths in series of twins discordant for smoking habits. The straightforward causal hypothesis predicts that deaths will occur earlier, on the average, in the smoking members of both monozygotic and dizygotic twin pairs. The constitutional hypothesis predicts that "early deaths" will occur with equal frequency, on the average, among the smoking and the non-smoking members of monozygotic twin pairs: where dizygotic twins are concerned, smokers should suffer an excess frequency of "early deaths" over non-smokers.

This simple test of the two hypotheses is, of course, hindered by the rarity of monozygotic twins discordant for smoking habits: only some 20–25% have been found to be strikingly discordant.[1,2]

Despite this obstacle, Friberg et al.[3] have obtained some intriguing results. They studied deaths among 246 male and 326 female monozygotic twin pairs, and in 706 male and 781 female dizygotic twin pairs appreciably discordant ("non-smoker" versus "smoker"; "less exposed" versus "more exposed"), and born in Sweden between 1901 and 1925. Among the dizygotic male twins, deaths were recorded over a standard period as follows: 13 of the "non-exposed and less-exposed" as compared with 34 of the "smoker and more exposed". Among dizygotic female pairs, deaths were recorded in 18 of the "non-exposed and less-exposed" and 20 of the "smoker and more exposed". Results for discordant monozygotic twins were very interesting: 14 deaths were recorded among the "non-exposed and less-exposed" men, but only 9 among the "smokers and more exposed"; among the women, 4 of the "non-exposed and less-exposed" and 6 of the "smoker and more exposed" died. Overall, the "more exposed" (sexes combined) enjoyed a slight but not significant advantage (18/15) over the "non-exposed and less-exposed". On a formal statistical test, the difference in mortality ratios ("non-exposed and less-exposed"/"smoker and more exposed") between the sets of monozygotic and dizygotic male twins corroborates the constitutional hypothesis and rejects (at the 1–2% level) the causal hypothesis (x^2 with Yates' correction = 5·78; $0{\cdot}01 < P < 0{\cdot}02$). However, this result needs to be treated with caution because the degree of discordance for smoking habits between the monozygotic and dizygotic series, although similar, was probably not identical. This reservation apart, the independent findings of Friberg et al.[3] support Dr. Seltzer.

Perhaps the issue could be put beyond reasonable doubt by supplementing the study of Friberg and his colleagues [3] with a world-wide survey under the ægis, say, of the World Health Organisation? And why should not the cigarette manufacturers foot the bill?

General Infirmary,
Leeds LS1 3EX. P. R. J. BURCH.

SMOKING AND HEALTH

SIR,—Professor Burch (June 10, p. 1283) would not have felt that critics of Dr. Seltzer's comments (Jan. 29, p. 243) on evidence concerning changes in mortality-rates of doctors and other men in England and Wales have been silent if he had given more weight to the leading article which you published in the same number as Dr. Seltzer's article (p. 238). Dr. Seltzer's letter (March 11, p. 586) was based on death-rates at all ages and was thus irrelevant to an argument based on changes in death-rates at ages at which stopping smoking could be expected to affect mortality, and thus required no answer. The observations of Friberg et al., which Professor Burch finds so impressive, are very interesting. Since these are based on a very small number of deaths and are in conflict with such a vast array of contrary evidence, it would be unwise to conclude that this evidence alone is valid and all the rest is invalid. If Professor Burch is unaware of other evidence about the constitutional hypothesis, he will find simple statements about it in the Royal College of Physicians' report [1] and more detailed reviews in the Surgeon-General's publications (The Health Consequences of Smoking)—in particular the recent 1971 and 1972 editions.[2,3] I agree with Professor Burch's suggestion that there should be more extensive surveys of mortality in twins with contrasting smoking habits. The difficulty is that these would have to be very large studies, because identical twins tend to have such similar smoking habits that pairs with widely contrasting smoking habits form a very small proportion of the total.

Department of Medicine,
Royal Postgraduate Medical School,
Hammersmith Hospital,
London W.12.

C. M. FLETCHER,
Secretary,
Royal College of Physicians'
Committee on Smoking
and Health.

SMOKING AND HEALTH

SIR,—In your issue of April 29 (p. 960) you published a letter from Dr. Theodore Sterling, of the Department of Applied Mathematics and Computer Science, Washington University, in which he quoted extensively from my articles. According to Sterling the excerpts selected lent support to Seltzer's conclusion (p. 243) that a proper analysis would not show any appreciable difference between the trends in mortality of doctors—many of whom have stopped smoking—and men of the same ages in England and Wales whose smoking habits have remained relatively unchanged. I cannot agree with this contention.

In a letter to *The Lancet* on Feb. 8 (p. 322) I pointed out that the trend of mortality with time after smoking is stopped varies with the nature of the disease, and that in the doctors we had studied the mortality from illnesses related to smoking fell by 38% after 10 or more years. This, Sterling asserts, is contradicted by another statement that after smoking is stopped the incidence of lung cancer remains practically the same as it was at the time of stopping.[1] The reason for the apparent contradiction would not be obvious to anyone who read only these selected statements. It should, however, have been obvious to a mathematician who read them in the context in which they were written. The first statement referred to mortality-rates standardised for age; that is, it compared mortality among men of the same ages. The second referred to the change in the incidence of disease with the passage of time; that is, it compared incidence among men of different ages. Since lung cancer and other diseases related to smoking increase in incidence with age, the two statements are perfectly compatible, and the assertion that Seltzer's conclusion (v.s.) "had been quietly conceded by others, foremost of whom is Doll," is false.

Sterling then quoted me as having reported a decline in cigarette consumption among men in the United Kingdom[2]; which, he said, again supported Seltzer and contradicted your editorial (p. 238). In fact what your editorial said was that the consumption of cigarettes had declined more in doctors than in other men. Nothing I have written contradicts that. No-one disputes the fact that the amount of tobacco smoked by men in Britain has declined since 1960 largely as a result of the introduction of filter-tipped cigarettes. The figures have been published by the Tobacco Research Council and are there for everyone to see,[3] and it is interesting to observe that the mortality from lung cancer in Britain has declined in men under 55 years of age while it has continued to increase at all ages in women, among whom tobacco consumption has continued to increase.

Finally, Sterling refers to the fact that some 30% of the doctors to whom Bradford Hill and I wrote failed to reply, and uses it to cast doubt on the validity of the comparison between the trend in the mortality of those doctors who did reply and the trend in the general population.

The failure to obtain a reply from a substantial proportion of the doctors to whom we originally wrote makes it dangerous to generalise from the respondents to doctors as a whole, as we have repeatedly pointed out.[4] We showed that the doctors who did reply were somewhat healthier than average, so that the mortality-rates among them were at first abnormally low.[4] This bias, however, had largely worn off after 2 years, so that we needed to exclude the first two years' observations from our comparison of trends. From then on the relevant fact is that we were able to keep 99·9% of the doctors under observation for the succeeding 12 years. Doubtless better material could be collected, but I am not convinced that the shortcomings of ours are so great that "not much can be learned" from it.

13 Norham Gardens,
Oxford.

RICHARD DOLL.

Coronary Heart Disease Morbidity

Tables 4 and 5 list the prospective studies carried on in a number of countries to identify the risk of CHD morbidity incurred by smoking. Here, CHD morbidity includes myocardial infarction as well as angina pectoris. Certain studies, notably those of Doyle, et al. (*54*), Keys, et al. (*111*), and Taylor, et al. (*183*) include a number of CHD deaths in their data that could not be separated out using the information provided in their respective reports. As noted in the discussion on CHD mortality, the CHD risk ratio increases significantly as the number of cigarettes smoked per day increases. Similarly, the HIP data of Shapiro, et al. (*172*) show that the elevated morbidity ratios declined with increasing age as has been shown for mortality ratios.

A recent monograph edited by Keys (*111*) dealt with the 5-year CHD incidence in males age 40 to 59 from seven countries. As summarized in table 4, cigarette smoking was found to be associated with an increased incidence of CHD in the U.S. railroad worker population, 2,571 individuals (*183*). None of the differences in ratio between smokers and nonsmokers was statistically significant for the 13 other population samples which varied in size from 505 to 982 individuals, from the five other countries. (Smoking was not considered in the two Japanese populations.) When more cases become available to provide greater statistical stability to the rates, this intercultural comparison should prove illuminating.

The results of those studies which have separated out angina pectoris as a manifestation of CHD are presented in table 5. Doyle, et al. (*54*) found no relationship between this manifestation of CHD and cigarette smoking. Both Jenkins, et al. (*90*) and Kannel, et al. (*94*) observed increased risk ratios among male cigarette smokers although these differences were not statistically significant. More recently, Shapiro, et al. (*172*) found a significantly increased risk for angina among their male cigarette smokers as well as increasing risk ratios with increasing dosage among both males and females, particularly in the younger age groups. A variety of hypothetical explanations have been advanced to account for this seeming contradiction. Among these are the relatively small number of cases, the difficulties associated with the definitive diagnosis of the syndrome, and differences in the methods of classifying those cases of angina pectoris which are followed by myocardial infarction.

Retrospective Studies

Table A6 presents data from the various retrospective studies of CHD prevalence. Most of these are case-control studies and show an increased percentage of smokers among those with clinical CHD when compared with a selected control population, usually without apparent CHD. Two of these studies include data on mortality.

The Interaction of Cigarette Smoking and Other CHD Risk Factors

The preceding section has reviewed the epidemiologic evidence which supports the judgment that cigarette smoking is a significant risk factor in the development of CHD. Many of the studies discussed above have identified a number of biochemical, physiological, and environmental factors, other than cigarette smoking, which also increase the risk of developing CHD. These risk factors include elevated serum lipids (particularly serum cholesterol) and hypertension, which, with cigarette smoking, are considered to be of greatest importance. Other factors are obesity, physical inactivity, elevated resting heart rate, diabetes (as well as asymptomatic hyperglycemia), electrocardiographic abnormalities, and a positive family history of premature CHD (*88*).

A number of these studies have also found that these factors, when present in the same individual, exert a combined effect on the risk of developing CHD. Figures 1 through 3 depict this interaction of risk factors. As may be noted in Figures 1 and 2, the additional factor of smoking greatly increases the risk of developing CHD among those people already at high risk because of other factors.

Furthermore, these studies have shown that the effect of smoking on the risk of developing CHD is statistically independent of the other risk factors. That is, when the effect of the other factors is statistically controlled, smoking continues to exert a significant effect on increasing the risk of developing and dying from CHD.

(111) Keys, A. (Editor). Coronary Heart Disease in Seven Countries. Circulation 41(4, Supplement 1): 1970. 211 pp.

(183) Taylor, H. L., Blackburn, H., Keys, A., Parlin, R. W., Vasquez, C., Puchner, T. Five-year follow-up of employees of selected U.S. railroad companies. IN: Keys, A. (Editor). Coronary Heart Disease in Seven Countries. American Heart Association Monograph No. 2, 1970. pp. 20–39.

(172) Shapiro, S., Weinblatt, E., Frank, C. W., Sager, R. V. Incidence of Coronary Heart Disease in a Population Insured for Medical Care (HIP). Myocardial infarction, angina pectoris, and possible myocardial infarction. American Journal of Public Health and the Nation's Health 59(6): Supplement to June 1969. 101 pp.

(90) Jenkins, C. D., Rosenman, R. H., Zyzanski, S. J. Cigarette smoking. Its relationship to coronary heart disease and related risk factors in the Western Collaborative Group Study. Circulation 38(6): 1148–1155, December 1968.

Smoking and Serum Lipids

The interaction of smoking and serum lipid levels in the development of CHD should be considered in the light of information concerning the relationship of smoking to serum lipid levels. Table A7 presents studies which deal with the association between smoking and lipids, notably cholesterol, triglycerides, and lipoproteins (concerned with lipid transport). While some of the studies have indicated that smokers show increased serum levels of these lipid constituents, others have not. The populations investigated and the methods of the various studies show significant variation. This lack of comparability makes interpretation of the findings difficult.

It is clear, however, that in the presence of high serum cholesterol, cigarette smoking increases the risk of CHD. Figure 4 depicts the data from the Chicago Peoples Gas, Light and Coke Company study which show that smoking greatly increases the risk of CHD in each of the cholesterol groups.

Smoking and Hypertension

Some epidemiological studies have indicated that smokers tend to have lower mean systolic and/or diastolic blood pressures than nonsmokers, while other studies have not found this to be the case (table A8). Reid, et al. (*155*), in a study of 1,300 British and American postal workers, found that the blood pressure difference between the smoking and nonsmoking groups was eliminated after controlling for body weight.

Tables 9 through 11, derived from the study by Borhani, et al. (*27*), demonstrate the following associations: That for both smokers and nonsmokers, the risk of dying from CHD increases with increasing diastolic or systolic pressure, and that the risk of mortality from CHD is higher among smokers than among nonsmokers in each blood pressure group. Cigarette smoking, therefore, has been shown to elevate CHD mortality independently both of its effect on blood pressure and of the effect of hypertension on CHD.

Smoking and Physical Inactivity

The recent study by Shapiro, et al. (*172*) of more than 110,000 persons participating in the Health Insurance Plan of New York City has further identified and elaborated upon the interaction of the various risk factors. Physical inactivity, both in employment and during leisure time, was found to be a potent risk factor for the development of CHD, particularly for rapidly fatal myocardial infarction.

Figure 5 depicts the effect which smoking exerts on CHD in combination with physical inactivity. Of note, also, is the observation that within each activity grouping, smoking greatly increases the risk of myocardial infarction, thus exerting an independent effect.

Smoking and Obesity

The analysis by Truett, et al. (*190*) of the risk factor data from the Framingham study revealed that weight, while a significant risk factor, had a considerably smaller effect on CHD incidence than serum cholesterol, cigarette smoking, or elevated blood pressure. The results concerning the interaction of smoking and obesity from the San Francisco longshoremen study are shown in table 12.

(155) Reid, D. D., Holland, W. W., Rose, G. A. An Anglo-American cardiovascular comparison. Lancet 2(7531): 1375–1378, December 30, 1967.

(27) Borhani, N. O., Hechter, H. H., Breslow, L. Report of a 10-year follow-up study of the San Francisco longshoremen. Mortality from coronary heart disease and from all causes. Journal of Chronic Diseases 16: 1251–1266, 1963.

(190) Truett, J., Cornfield, J., Kannel, W. A multivariate analysis of the risk of coronary heart disease in Framingham. Journal of Chronic Diseases 20: 511–524, 1967.

TABLE 9.—*Death rates from coronary heart disease, by systolic blood pressure: ILWU mortality study 1951–61*
(Coronary heart disease as classified under ISC Code 420)

Age group	Systolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–64	<130	1,517	27	2,413	8
	130–149	2,026	84	2,012	17
	150–169	740	95	1,177	26
	>170	369	109	672	45
65–64	<130	1,057	84	1,850	[2]6
	130–149	1,350	94	2,401	[2]25
	150–169	647	93	1,858	45
	>170	524	210	1,117	125

[1] Rate per 10,000 person-years of observation.
[2] $p<0.025$.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 10.—*Death rates from coronary heart disease, by diastolic blood pressure: ILWU mortality study, 1951–61*
(Coronary heart disease as classified under ISC Code 420)

Age group	Diastolic blood pressure in 1951	Smokers: Person-years of observation	Smokers: Death rate[1]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[1]
45–64	<80	1,527	26	1,700	6
	80– 89	2,115	47	2,947	17
	90– 99	961	52	1,507	33
	>100	449	89	1,020	29
65–64	<80	1,059	104	1,447	[2]21
	80– 89	1,521	89	2,704	15
	90– 99	869	194	1,521	[2]48
	>100	369	163	954	147

[1] Rate per 10,000 person-years of observation.
[2] $p<0.05$.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 11.—*Death rates from coronary heart disease, among hypertensives and nonhypertensives: ILWU mortality study, 1951–61*
(Coronary heart disease as classified under ISC Code 420)

Age group	Blood pressure status[1]	Smokers: Person-years of observation	Smokers: Death rate[2]	Nonsmokers: Person-years of observation	Nonsmokers: Death rate[2]
45–64	Hypertensives	883	125	1,871	[3]32
	Nonhypertensives	4,169	29	5,303	13
65–64	Hypertensives	931	180	2,219	95
	Nonhypertensives	2,657	93	4,407	[3]16

[1] According to the WHO recommendation, the following cut-off points are recommended for the definition of hypertension:
(1) Normotension—below 140/90 mm. Hg.
(2) Hypertension—systolic blood pressure 160 mm. Hg. or over, or diastolic 95 mm. Hg. or over, or both.
(3) Borderline—the residual category. In this analysis, Normotensives and Borderlines were combined and the population was grouped into 'Nonhypertensives' (1 and 3) and 'Hypertensives' (2).
[2] Rate per 10,000 person-years of observation.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

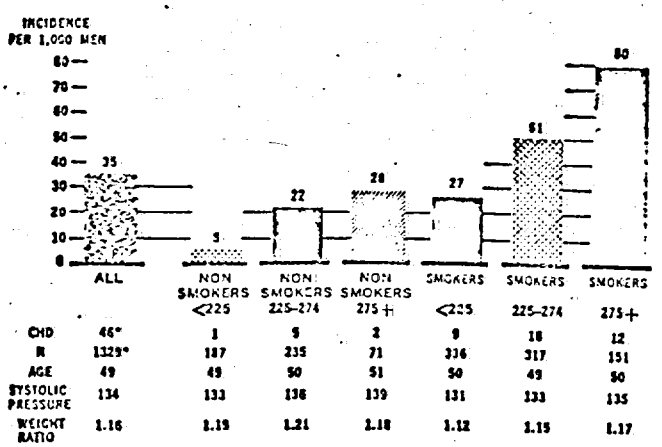
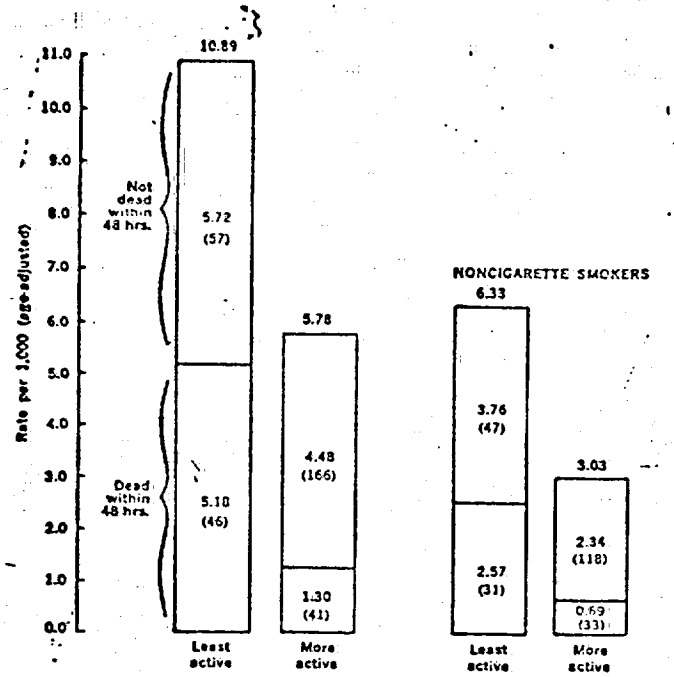


FIGURE 4—Relationship between smoking status and serum cholesterol level at initial examination, and incidence of clinical coronary heart disease in men originally age 40–59, free of definite CHD, and followed subsequently without systematic intervention, Peoples Gas Light and Coke Company study, 1958–1962. *For 34 men, no information on smoking status was available; one of these men had a coronary episode.
SOURCE: Stamler, J., et al. (177).



Note: Both for cigarette smokers and noncigarette smokers differences between rates among the least and more active men are statistically significant for total MI and rapidly fatal MIs at the 0.99 confidence level. For other MIs the difference is statistically significant only for the nonsmokers (confidence level 0.95).

FIGURE 5—Average annual incidence of first myocardial infarction among men in relation to overall physical activity class and smoking habits (age-adjusted rates per 1,000)

(Actual number of deaths or myocardial infarctions are represented by figures in parentheses)

SOURCE: Shapiro, S., et al. (*172*).

This table shows that cigarette smokers in the 55 to 64 year age group were observed to have higher CHD death rates than nonsmokers in all weight categories. Similar findings, although not in all weight groups, were observed for the 45 to 54 year age group. Cigarette smoking is thus shown to be a CHD risk factor independent of body weight.

Smoking and Electrocardiographic Abnormalities

Electrocardiographic (ECG) abnormalities such as T-wave and ST-segment changes as well as a number of arrhythmias are useful indicators of CHD and may, therefore, be predictive of the development of clinically overt CHD manifestations. The results summarized in table 13, from the prospective study by Borhani, et al. (*27*), reflect the joint predictive value of smoking and ECG abnormalities on the death rate from CHD.

Smoking and Heart Rate

Recent analysis by Berkson, et al. (*23*) of the data derived from the Chicago Peoples Gas, Light and Coke Company study of middle-aged men revealed that resting heart rates of 80 or greater were associated with an increase in the risk of death from CHD. These authors found that this association was independent of the other major coronary risk factors.

Table 14 presents the interaction between smoking, blood pressure, and elevated heart rate in increasing the risk of CHD mortality. This study shows that cigarette smoking increases CHD risk in the presence of elevated heart rate as well as in its absence.

(*23*) BERKSON, D. M., STAMLER, J. LINDBERG, H. A., MILLER, W. A., STEVENS, E. L., SOYUGENIC, R., TOKICH, T. J., STAMLER, R. Heart rate: An important risk factor for coronary mortality—ten-year experience of the Peoples Gas Co. Epidemiologic study (1958–68). IN: Jones, R. J. (Editor). Atherosclerosis. Proceedings of the Second International Symposium. New York, Springer-Verlag, 1970. pp. 382–389.

TABLE 12.—*Death rates from coronary heart disease among men without abnormalities related to cardiopulmonary diseases by weight classification in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Weight classification [1]	Smokers		Nonsmokers	
		Person-years of observation	Death rate [2]	Person-years of observation	Death rate [2]
45–54	Not overweight	385	21	279	7
	Slightly overweight	962	28	1,036	0
	Moderately overweight	1,333	25	1,574	25
	Markedly overweight	1,055	22	1,797	0
55–64	Not overweight	222	42	247	0
	Slightly overweight	536	75	605	26
	Moderately overweight	855	109	1,320	[3]11
	Markedly overweight	736	88	1,653	[3]12

[1] The four classes are defined in the text.
[2] Rate per 10,000 person-years of observation.
[3] $p<0.01$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 13.—*Death rates from coronary heart disease, by electrocardiographic findings in 1951: ILWU mortality study, 1951–61*

(Coronary heart disease as classified under ISC Code 420)

Age group	Electrocardiographic findings in 1951	Smokers		Nonsmokers	
		Person-years of observation	Death rate [1]	Person-years of observation	Death rate [1]
45–54	Abnormal	586	102	1,020	39
	Normal	4,454	38	6,134	15
55–64	Abnormal	583	223	1,149	96
	Normal	3,031	88	5,479	[2]31

[1] Rate per 10,000 person-years of observation.
[2] $p<0.025$.
SOURCE: Borhani, N. O., et al. (27).

TABLE 14.—*1958 status with respect to heart rate, blood pressure, cigarette smoking, and 10-year mortality rates, by cause (1,529 men originally age 40–59 and free of definite coronary heart disease) Peoples Gas Co. Study, 1958–68*

1958 risk factor status				Ten-year mortality, 1958–68			
				All causes		CHD	
Heart rate	Cigarette smoking	Diastolic pressure	Number of men	Number	Rate	Number	Rate
NH	NH	NH	378	20	[1]48.3	5	[1]12.0
H	NH	NH	45	6	114.9	3	70.3
NH	NH	H	107	14	118.3	6	51.8
H	NH	H	30	8	221.6	3	82.0
NH	H	NH	491	57	115.2	19	38.9
H	H	NH	127	22	171.1	8	62.3
NH	H	H	103	22	190.4	6	55.0
H	H	H	44	13	265.4	5	94.9
All			[2]1,325	162	113.2	65	39.4

[1] Rate per thousand. All rates are age-adjusted by 5-year age groups to U.S. male population, 1960. High (H): Heart rate ≧80; ≧10 cigarettes per day; diastolic blood pressure ≧90 mm. Hg. NH is not high, i.e., below specified cutting points.
[2] No smoking data available on 4 of the 1,329 men.
SOURCE: Berkson, D. M., et al. (28).

TABLE 15.—*The effect of the cessation of cigarette smoking on the incidence of CHD*

(Incidence ratios—actual number of cases or events are shown in parentheses)

Author, year, country, reference	Results		Comments
	All CHD events	*All myocardial infarction*	
Jenkins et al., 1968, U.S.A. (90).	Never smoked 1.00 (30)	1.00 (21)	
	Current cigarette smokers 2.35 (84)	2.79 (63)	
	Former cigarette smokers 2.16 (19)	2.47 (15)	
	Death from CHD		
	Smoked 1–19 cigarettes/day	*Smoked >19 cigarettes/day*	
Hammond and Garfinkel, 1969, U.S.A. (77).	Never smoked regularly 1.00 (1,341)	1.00 (1,341)	Male data only
	Current cigarette smokers 1.30 (1,065)	2.55 (2,972)	
	Stopped <1 year 1.42 (29)	1.81 (62)	
	1–4 ..... 1.22 (57)	1.51 (158)	
	5–9 ..... 1.26 (63)	1.18 (135)	
	10–19 ..... 0.98 (63)	1.25 (135)	
	>20 ..... 1.03 (70)	1.05 (101)	
	All ex-cigarette smokers 1.16 (263)	1.25 (564)	
	Total definite myocardial infarction		
Shapiro et al., 1968, U.S.A. (172).	Never smoked 1.00		
	Current cigarette smokers 1.81		
	Stopped ≤5 years 0.76		
	All CHD deaths	*First major coronary event*	
Pooling Project, American Heart Association 1970, U.S.A. (84).	Never smoked 1.00 (27)	1.00 (33)	See table 4 for description of Pooling Project.
	>½ pack/day 1.65 (34)	1.65 (72)	
	1 pack/day 1.70 (86)	2.88 (205)	
	>1 pack/day 3.00 (45)	3.25 (154)	
	Ex-smokers 0.80 (19)	1.28 (61)	

TABLE 16.—*Annual probability of death from coronary heart disease, for current and discontinued smokers, by age, maximum amount smoked, and age started smoking*

Age	Maximum daily number of cigarettes smoked	Age started smoking: 15–19 — Current smokers	15–19 — Discontinued for five or more years (Probability X10⁴)	20–24 — Current smokers	20–24 — Discontinued for five or more years
55–64	0	691	—	691	—
	10–20	798	648	811	651
	21–39	869	764	872	698
65–74[1]	0	1,016	—	1,015	—
	10–20	1,501	1,169	1,478	1,213
	21–39	1,518	1,334	1,573	1,098

[1] For age group 65–74, probabilities for discontinued smokers are for 10 or more years of discontinuance since data for the 5–9 year discontinuance group are not given.

SOURCE: Cornfield, J., Mitchell, S. (45).
Based on data derived from Kahn, H. A. (93).

THE EFFECT OF CESSATION OF CIGARETTE SMOKING ON CORONARY HEART DISEASE

A number of epidemiological studies have been concerned with the CHD incidence and mortality among ex-cigarette smokers as compared with current smokers (*51, 76, 88, 90, 93, 172*). These studies are listed in table 15. Table 16 presents the data derived by Cornfield and Mitchell (*45*) from the Dorn Study of U.S. Veterans (*93*).

Ex-cigarette smokers show a reduced risk of both myocardial infarction and death from CHD relative to that of continuing cigarette smokers. The Pooling Project (*83*) and the Western Collaborative Study Group (*192*) which adjusted for the other risk factors of elevated serum cholesterol and blood pressure observed this relationship. Hammond and Garfinkel (*76*) noted that cessation of smoking is accompanied by a relative decrease in risk of death from CHD within 1 year after stopping.

This decreased risk of CHD among ex-smokers further strengthens the relationship between smoking and CHD. It must be noted, however, that the group of ex-smokers is composed of individuals who have stopped smoking for a variety of reasons. Those who stop because of ill health and the presence of symptoms are generally at high risk and can bias the group results in one direction; those healthy persons who stop as part of a general concern about their health and may adopt a number of self-protective health practices are generally at low risk and can bias the group results in the other direction. Therefore, ex-smokers as a group are not fully representative of the entire population of smokers and may have limited value in predicting what would happen if large numbers of cigarette smokers stopped smoking purely for self-protection. Certain incidence studies, such as the Pooling Project (*83*), were initiated with only clinically healthy individuals. The data from such studies, as well as those from the British physicians study, contain ex-smoker data less influenced by these biases.

(45) CORNFIELD, J., MITCHELL, S. Selected risk factors in coronary disease: Possible intervention effects. Archives of Environmental Health 19(3): 382–394, September 1969.

(51) DOLL, R., HILL, A. B. Mortality in relation to smoking: 10 years' observations of British doctors. (Concluded) British Medical Journal 1(5396): 1460–1467. June 6. 1964.

(76) HAMMOND, E. C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Archives of Environmental Health 19(2): 167–182, August 1969.

(192) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.

Fletcher and Horn (*63*) have recently presented data derived from the British physicians study of Doll and Hill. Over the past 10-15 years, cigarette smoking rates among British physicians have declined significantly in comparison with those of the general British population. The information presented by these authors concerning all cardiovascular diseases showed that for individuals between the ages of 35 and 64, the age-adjusted death rate for CHD declined by 6 percent among physicians and rose by 10 percent among the male population of England and Wales during the period from 1953–57 to 1961–65.

(*63*) FLETCHER, C. M., HORN, D. Smoking and health. WHO Chronicle 24(8): 345–370, August 1970.

THE CONSTITUTIONAL HYPOTHESIS

The effect of smoking on the incidence of CHD has been found to be independent of the influence of the other CHD risk factors. When such risk factors as high serum cholesterol (*177*), increased blood pressure (*27*), elevated resting heart rate (*23*), physical inactivity (*172*), obesity (*27*), and electrocardiographic abnormalities (*27*) have been controlled, cigarette smokers still show higher rates of CHD than nonsmokers.

It has been suggested by some (*39, 170*) that the relationship between cigarette smoking and CHD has a constitutional basis. That is people with certain constitutional make-ups are more likely to develop CHD, and the same people are more likely to smoke cigarettes. This hypothesis maintains that the relationship between cigarette smoking and CHD is thus largely fortuitous and that the significant relationships are between the genetic make-up of the individual and CHD and between the genetic make-up of the individual and his becoming a cigarette smoker. Two sets of epidemiologic data bear on this hypothesis.

It has been maintained that people with a certain temperament are more likely to smoke and also more likely to develop CHD. These characteristics have been demonstrated for those with the Type A behavior pattern of Rosenmann, et al. (*159*) which is characterized by competitiveness, excessive drive, and an enhanced sense of time urgency. The prospective study organized by the Western Collaborative Group indicates that individuals who exhibit this type of personality are more likely to have or develop CHD than those without it (Type B), whether or not they smoke. When the incidence rates of CHD are analyzed with respect to smoking and personality types (tables A17, A18), it is noted that in both Type A and Type B individuals the incidence of CHD is greater among cigarette smokers than among nonsmokers. This research indicates that both personality type, as measured in these studies, and cigarette smoking contribute independently as risk factors to the development of CHD. To what extent such behavior patterns are determined constitutionally or represent acquired characteristics is still open to question.

The other type of research designed to study the genetic hypothesis has made use of data from registries of twins. Cederlof, et al. (*37, 38, 39, 40*) have utilized the Twin Registries of Sweden and the Veterans Follow-Up Agency of the U.S. National Academy of Sciences–National Research Council to investigate the relative contributions of heredity and smoking to cardiovascular and bronchopulmonary symptom prevalence. Data obtained by mailed questionnaires were analyzed for the following characteristics: zygosity of the same-sex twin pair, urban-rural residence differences, smoking concordance, and history of various symptoms. Comparisons were made between smoking discordant monozygotic (identical) pairs and smoking discordant dizygotic (fraternal) pairs, and between unmatched twin pairs and matched twin pairs. Smoking discordance has been defined somewhat differently in various reports but, in general, describes twin pairs in which the smoking habits differ between the two members of the same twin pair.

(*39*) CEDERLOF, R., FRIBERG, L., JONSSON, E., KAIZ, L. Respiratory symptoms and "angina pectoris" in twins with reference to smoking habits. An epidemiological study with mailed questionnaire. Archives of Environmental Health 13 (6): 726–737, December 1966.

(*159*) ROSENMAN, R. H., FRIEDMAN, M., STRAUS, R., WURM, M. KOSITCHEK, R., HAHN, W., WERTHESSEN, N. T. A predictive study of coronary heart disease. The Western Collaborative Group Study. Journal of the American Medical Association 189(1): 15–22, July 6, 1964.

(*37*) CEDERLOF, R. The Twin Method in Epidemiological Studies on Chronic Disease. Institute of Hygiene of the Karolinska Institute, Department of Environmental Hygiene of the National Institute of Public Health, Department of Sociology, University of Stockholm, Stockholm, 1966. 71 pp.

(*38*) CEDERLOF, R., FRIBERG, L., HRUBEC, Z. Cardiovascular and respiratory symptoms in relation to tobacco smoking. A study on American twins. Archives of Environmental Health 18(6): 934–940, June 1969.

(*40*) CEDERLOF, R., JONSSON, E., LUNDMAN, T. On the validity of mailed questionnaires in diagnosing "angina pectoris" and "bronchitis". Archives of Environmental Health 13(6): 738–742, December 1966.

Analyzing the data obtained from 9,319 Swedish twin pairs (72.3 percent of the possible respondents), Cederlof, et al. (*89*) found that respiratory symptoms were more common among smokers in both the unmatched and matched smoking discordant twin pair groups. The authors analyzed the data in two distinct manners. Group A analysis, which did not control for genetic factors utilized two groups; the first composed of all the firstborn, and the second of those listed second on the birth certificates. Group B analysis utilized MZ and DZ twin pairs which were discordant for smoking, thereby controlling genetic factors. "Angina pectoris," as defined by a certain pattern of responses to the questionnaire, was found to be more prevalent among smokers in Group A, but this difference was not present when the data from Group B were analyzed. Males in the first group exhibited a "hypermorbidity ratio" of 1.6, while those in the second group were found to have one of approximately 1.1. The authors concluded that this difference between the two groups provides better support for the importance of constitutional factors as against the importance of cigarette smoking in the development of angina pectoris.

A similar study was done using the responses of 4,379 U.S. Veteran twin pairs (approximately 60 percent of estimated available total) who completed the mailed questionnaires (*88*). Cederlof, et al. found a significantly increased prevalence of chest pain and "angina pectoris" among smokers when Group A was analyzed. Analysis of the smoking-discordant matched twin pairs (Group B) revealed no association between smoking and cardiovascular symptoms among the monozygotic pairs. The dizygotic pair data did show a slight association. The authors concluded that this lack of association among the monozygotes and its presence among the dizygotes and unmatched pairs strengthens the case for a constitutional hypothesis.

A major problem in these studies is the small number of cases available and, therefore, the statistical instability of the results. In the Swedish study, among the 274 monozygotes, only 19 smokers and 16 nonsmokers were classified as having angina pectoris while among the 733 dizygotes, 25 smokers and 25 nonsmokers were so classified. In neither group was the difference between the prevalence ratios found in the Group A analysis and that in the Group B analysis of statistical significance. Analysis of the data on women shows a similar lack of significance.

Similar criticisms may be made of the study which utilized the U.S. Veteran Twin Registry. In that study, the authors observed that the difference in the prevalence of angina pectoris between the low-cigarette-exposure and high-cigarette-exposure dizygotic groups was not present among the monozygotes. The authors questioned whether the excess morbidity associated with cigarette smoking found in the dizygotic group was causal as it was not possible to reproduce the association when studying monozygotic smoking-discordant twin pairs. As noted above, the numbers in this study are also small so that the differences in rates do not approach statistical significance.

Tibblin (*188*) has questioned the value of a mailed questionnaire to diagnose heart disease. The questionnaire as originally constructed was used and validated by interview technique alone (*157*, *158*). Cederlof, et al. (*40*) conducted a study to determine the validity of this questionnaire as a mailed instrument by personally interviewing and examining 170 of the twin pairs who had replied. Of the eight males who were diagnosed as having "angina pectoris" by the questionnaire, four were found to be free of symptoms on clinical examination, while among 204 responding negatively, two were found to have angina by clinical criteria. None of the 11 women who were diagnosed as positive by questionnaire was found to be clinically affected, and of the 136 reporting as negative, three had symptoms of angina pectoris.

Other major difficulties associated with these studies include the problems of using prevalence data in the investigation of a disease (CHD) from which a significant number of those affected die shortly after the onset of symptoms, the inclusion of ex-smokers in the smoking population, and the low numbers of heavy cigarette smokers in the Swedish population.

In general, the problems of using twin registries to study the etiology of cardiovascular disease with mortality and morbidity ratios in the neighborhood of 2 to 1 are much more difficult than in studying the etiology of bronchopulmonary disease in which the relationships are of the order of magnitude of 4 to 1.

8) TIEBLIN, G. Kommentar till en svensk tvillingundersökning. (Comment on research on twins in Sweden.) Lakartidningen 65 (47): 4654–4655, November 20, 1968.

(*157*) ROSE, G. A. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bulletin of the World Health Organization 27(6): 645–658, 1962.

(*158*) ROSE, G. A. Chest pain questionnaire. Milbank Memorial Fund Quarterly 43(2, part 2): 32–39, April 1965.

Twin Registry. The criticisms of the Twin Registry noted here should also be compared with a subsequent letter by Burch (Lancet 1: 1283, 1972) and Letters to the Editor from Cherry and Forbes (Lancet 14 October, 1972) and Friberg (Lancet 4 November 1972). These are reproduced below.

SMOKING AND HEALTH

SIR,—Are we to judge from their silence that Dr. [illegible]'s critics have conceded his case (Jan. 29, p. 243, and [illegible] 11, p. 586)? Is cigarette-smoking non-lethal?

[illegible]he undoubted positive associations between cigarette [illegible]ing and death-rates from various diseases are not [illegible]al in origin, an alternative explanation is needed. [illegible]rding to Fisher,[1] such associations might arise from [illegible]nstitutional factors. That is to say, one or more of the [illegible]s that predispose to certain forms of smoking might be [illegible]ame as, or linked with, genes that predispose to fatal [illegible]ders such as lung cancer. In principle, we can dis-[illegible]inate between causal and constitutional hypotheses by [illegible]mining deaths in series of twins discordant for smoking [illegible]. The straightforward causal hypothesis predicts [illegible] deaths will occur earlier, on the average, in the smoking [illegible]bers of both monozygotic and dizygotic twin pairs. [illegible] constitutional hypothesis predicts that "early deaths" [illegible]ccur with equal frequency, on the average, among the [illegible]ing and the non-smoking members of monozygotic [illegible] pairs: where dizygotic twins are concerned, smokers [illegible]ld suffer an excess frequency of "early deaths" over [illegible] smokers.

[illegible]is simple test of the two hypotheses is, of course, [illegible]ered by the rarity of monozygotic twins discordant [illegible] smoking habits: only some 20–25% have been found [illegible]e strikingly discordant.[1,2]

[illegible]espite this obstacle, Friberg et al.[3] have obtained some [illegible]ging results. They studied deaths among 246 male [illegible]126 female monozygotic twin pairs, and in 706 male [illegible]781 female dizygotic twin pairs appreciably discordant [illegible]on-smoker" versus "smoker"; "less exposed" [illegible]us "more exposed"), and born in Sweden between [illegible]0 and 1925. Among the dizygotic male twins, deaths [illegible]re recorded over a standard period as follows: 13 of [illegible]"non-exposed and less-exposed" as compared with [illegible]f the "smoker and more exposed". Among dizygotic [illegible]ale pairs, deaths were recorded in 18 of the "non-[illegible]osed and less-exposed" and 20 of the "smoker and [illegible]re exposed". Results for discordant monozygotic twins [illegible]re very interesting: 14 deaths were recorded among [illegible]e "non-exposed and less-exposed" men, but only 9 [illegible]ong the "smokers and more exposed"; among the [illegible]men, 4 of the "non-exposed and less-exposed" and 6 of [illegible]e "smoker and more exposed" died. Overall, the "more [illegible]osed" (sexes combined) enjoyed a slight but not signifi-[illegible]t advantage (18/15) over the "non-exposed and less-[illegible]posed". On a formal statistical test, the difference in mor-[illegible]ity ratios ("non-exposed and less-exposed"/"smoker [illegible]more exposed") between the sets of monozygotic and [illegible]ygotic male twins corroborates the constitutional hypo-[illegible]is and rejects (at the 1–2% level) the causal hypothesis [illegible]with Yates' correction = 5·78; $0{\cdot}01 < P < 0{\cdot}02$). How-[illegible]r, this result needs to be treated with caution because [illegible]e degree of discordance for smoking habits between the [illegible]nozygotic and dizygotic series, although similar, was [illegible]ably not identical. This reservation apart, the indepen-[illegible]t findings of Friberg et al.[3] support Dr. Seltzer.

[illegible]Perhaps the issue could be put beyond reasonable doubt [illegible]by supplementing the study of Friberg and his colleagues [illegible]by a world-wide survey under the ægis, say, of the World Health Organisation? And why should not the cigarette manufacturers foot the bill?

[illegible] General Infirmary, P. R. J. BURCH.

SMOKING AND HEALTH

SIR,—Professor Burch [1,2] calls for a worldwide twin study to distinguish between causal and constitutional factors in the association between cigarette smoking and disorders such as coronary heart-disease and lung cancer. This proposal is based on the results obtained by Friberg et al.[3] for monozygotic and dizygotic twins which suggest to Friberg and Burch that differences in mortality between populations of smokers and non-smokers are a consequence of differences in genetic and other inherited factors.

This interpretation of Friberg's results is open to several criticisms. First, the published data provide no direct information about differences in mortality within individual *pairs* of twins. That is, the data only provide information about deaths in two populations, each member of which happens to have a twin in the other population; it is not stated in how many instances both, one, or no twins in a pair have died. Hence, data pertaining comparisons within twin pairs, where one twin serves as a control for the other (which represents the unique value of this type of experiment), are not available to the reader. For example, for monozygotic twins, where Friberg observes approximately equal numbers of deaths for non-smokers and smokers—viz., 4 vs 5, and 4 vs 6 deaths, respectively; for males and females, it is possible that, on average, the smokers died at an early age.

Secondly, it must be noted that some of the reported data only represent approximations, since two groups of smokers have overlap; a "less exposed" group, which is considered with non-smokers, includes smokers of up to 20 cigarettes per day, whereas a "more exposed" group, which is considered with smokers, includes smokers of down to 10 cigarettes per day. Such an approach does not provide a clear distinction between categories of amounts smoked. Also, the intra-pair differences to smoking exposure might be less for the monozygotic than for the dizygotic pairs, because of constitutional factors which might influence smoking discordancy.

For these and other reasons, it is appropriate to re-examine the methods of presentation and analysis. A discussion along these lines has been presented previously.[4] Be-

---

cause linking cigarette smoking causally to various diseases has, for some time, been sufficiently strong to concentrate efforts on reducing or eliminating the hazards of cigarette smoking.[5–8] This conclusion does not deny the fact that there remain numerous questions concerning the action of cigarette smoking, which remain to be solved. One of these is the role of genetic factors which may contribute to a person taking up various forms of smoking or contracting individual diseases. A worldwide twin study, as suggested by Professor Burch, would take a number of years to complete; and since, at present, there is little evidence that such a study would alter the main conclusions concerning the effects of cigarette smoking on health, a lower priority should be given to such a study than to research on reducing the accepted hazards.

Department of Statistics,
University of Waterloo,
Waterloo, Ontario,
Canada.

W. H. CHERRY
W. F. FORBES.

SMOKING AND HEALTH

SIR,—In the comments of Dr. Cherry and Professor Forbes (Oct. 14, p. 824) on the proposal of Professor Burch [1,2] to embark on worldwide twin studies, our report from the Swedish registry on mortality in smoking discordant monozygotic and dizygotic twins [3] is criticised to some extent.

Dr. Cherry and Professor Forbes point out that the data provide no information on what has happened within the individual *pairs* of twins, since it was not stated in how many instances both, one, or no twins in a pair had died. We agree that such analysis is of importance where a substantial number of concordant deaths occur. Concerning the crucial group (male twin pairs born 1901–25), where differences between dizygotic and monozygotic twins were found, however, only one pair in the dizygotic group (non-smoker/smoker in age-group 1901–10) and one pair in the monozygotic group ("less exposed"/"more exposed" in age-group 1901–10) showed concordant death. Thus the findings reported actually refer to differences within individual *pairs* of twins. For our future reports, when a larger number of concordant deaths can be expected, no doubt one should also take the year of death into consideration. At the time of our report [3] such an analysis would not have been meaningful.

We appreciate the comments, but when Dr. Cherry and Professor Forbes mean that what they point out may invalidate our interpretation of the data presented, we must disagree. Also, we are surprised about their comments, because already, in a personal letter, Professor Forbes received a complete set of data showing the number of twins in the mentioned age-groups, divided into dizygotic and monozygotic pairs, from which it was easily seen in how many instances both, one, or no twins in a pair had died.

Dr. Cherry and Professor Forbes are sceptical of Professor Burch's proposal of worldwide twin studies. One reason given is that, at present, there is little evidence that such studies would alter the main conclusions concerning the effects of cigarette smoking on health. For certain pulmonary diseases (e.g., lung cancer) the causal relationship with cigarette smoking is quite clear. On the other hand, twin studies might well be of substantial value even for these effects—for example, to find out whether certain persons are more susceptible than others to an effect of cigarette smoking. For other effects, including high mortality in general and particularly, for example, in coronary heart-disease, we feel that the case against cigarette smoking per se is not all that strong and in our opinion international collaboration using twins as target populations would be extremely useful. The problem in twin studies, even using a population the size of Sweden's, is to get enough numbers in different, well-defined smoking discordant groups. We are happy to learn that Dr. Cherry and Professor Forbes do not live up to their own objections to creating new registries. As can be seen in a recent paper of theirs,[9] they state, "A twin study is being planned, partly to investigate further the observations, on smoking discordant twins, reported by Friberg et al."

Finally, we wish to point out that international collaboration on twin studies should not be carried out with the sole aim of studying effects of tobacco on health. Certainly, as was pointed out at an international symposium on twin registries in the study of chronic disease,[6] in advocating the establishment of new large-scale twin registries, it should be recognised that such registries constitute valuable national resources for investigations into the causes and prevention of disease. While large-scale twin studies until now have primarily focused on the health consequences of smoking, the twin method has a much broader applicability to a large number of medical and social problems concerned with the interrelationships between environmental agents and their impact upon the genetic constitution. The importance of these interrelationships was precisely the reason for a recent expansion of the Swedish twin registry in collaboration with the National Environment Protection Board to include an additional 15,000 pairs born from 1926 to 1942.

Department of Environmental Hygiene, Karolinska Institute, S-104 01 Stockholm 60, and Department of Environmental Hygiene, National Environment Protection Board, Stockholm 60, Sweden.

LARS FRIBERG.

More recently, Friberg, et al. (*69*) reported on mortality data from the Swedish Twin Registry. The authors suggested that part of the increased mortality observed among smokers when compared with nonsmokers was not due to smoking per se but to factors associated with smoking. The very small numbers of total deaths presently available (47 deaths among 706 dizygotic pairs and 13 deaths among 246 monozygotic pairs) do not provide a statistically stable base for deriving any conclusions at the present time.

(*69*) Friberg, L., Cederlof, R., Lundman, T., Olsson, H. Mortality, smoking discordant monozygotic and dizygotic twins. A study on the Swedish Twin Registry. Archives of Environmental Health 21(4): 508–513, October 1970.

Hauge, et al. (*81*) have recently reported on the influence of smoking on the morbidity and mortality observed in the Danish Twin Register. Among 762 monozygotic and same-sexed dizygotic twin pairs, angina pectoris was found to be significantly more frequent in those cotwins with a higher consumption of tobacco than in those with a lower or no consumption. A similar tendency was observed for myocardial infarctions but was not of statistical significance.

(*81*) Hauge, M., Harvald, B., Reid, D. D. A twin study of the influence of smoking on morbidity and mortality. Acta Geneticae Medicae et Gemellologiae 19: 335–336, 1970.

Seltzer, who has been a proponent of the constitutional hypothesis, in a recent review of some of the experimental, clinical, and pathological data relating smoking and CHD, concluded that the evidence from these areas has not "reasonably substantiated" the "hypothesis" of the acute effect of cigarette smoking on the coronary circulation, nor has the chronic effect of cigarette smoking on the cardiovascular system been shown to be a "clear" and consistent one (*170*). His views are contrary to those of most researchers in this field.

(*170*) Seltzer, C. C. The effect of cigarette smoking on coronary heart disease. Where do we stand now? Archives of Environmental Health 20(3): 418–423, March 1970.

Although the data from the twin studies are inconclusive with regard to a role for genetic factors in heart disease, it would be surprising if genetic factors did not play such a role. It is open to question whether findings from twin studies can be used to distinguish between the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors "cause" both heart disease and smoking.

EXPERIMENTAL STUDIES CONCERNING THE RELATIONSHIP OF CORONARY HEART DISEASE AND SMOKING

Several areas of interest in cardiovascular pathophysiology have been investigated in the search for the mechanisms by which cigarette smoking contributes to cardiovascular disease, particularly coronary artery disease. Previous Public Health Service Reviews (*191*, *192*, *193*, *198*) have described in detail and commented on the results of experiments by many teams of researchers.

(*191*) U.S. Public Health Service. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

(*193*) U.S. Public Health Service. The Health Consequences of Smoking. 1969 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696-2, 1969. 98 pp.

(*198*) U.S. Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

Central to the discussion which follows is a concept of cardiac physiology which provides a framework for analysis and understanding of the varied research. That concept concerns the dynamic balance between myocardial oxygen need and supply.

Cardiovascular Effects of Cigarette Smoke and Nicotine

The inhalation of tobacco smoke or the parenteral administration of nicotine has been found by many researchers to be associated with a number of specific acute cardiovascular responses. These responses have been observed in human as well as animal subjects, including increased heart rate, blood pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, myocardial oxygen consumption, arrhythmia formation, and electrocardiographic or ballistocardiographic changes (tables A 20 to A 22). The effect of these responses on coronary blood flow will be discussed in a following section.

That the acute effects observed following the inhalation of cigarette smoke are due primarily to the nicotine present in the smoke may be seen in the results of a number of experiments. In humans, Irving and Yamamota (*89*) and Von Ahn (*202*) duplicated the effects of cigarette smoking by the administration of nicotine intravenously. Similar results in animals were noted by Kien and Sherrod (*112*).

(*89*) Irving, D. W., Yamamoto, T. Cigarette smoke and cardiac output. British Heart Journal 25: 126–132, 1963.

(*202*) Von Ahn, B. Tobacco smoking, the electrocardiogram, and angina pectoris. Annals of the New York Academy of Sciences 90(1): 190–198, September 27, 1960.

Constitutional Hypothesis. The document has answered (170) Seltzer by stating that his views are contrary to those of most researchers in this field. The article is reproduced in its entirety.

The Effect of Cigarette Smoking on Coronary Heart Disease

Where Do We Stand Now?

Carl C. Seltzer, PhD, Boston

IT IS AN ESTABLISHED observation that there is a statistically significant association of cigarette smokers and increased mortality and morbidity from coronary heart disease (CHD) in men. It forms the basic springboard for public health warnings as to the health hazards of cigarette smoking and CHD. But it does not tell us how smoking causes or precipitates a death from CHD, or if indeed it does. The most such an observation can do is to demonstrate the existence of a relationship; it cannot establish any existing relationship as a causal one. For this, it is necessary to derive biological inferences from other evidence, pathological, clinical, experimental, as well as epidemiological. What follows is an analysis as to where we are now with respect to the biological inferences, and not necessarily where we will be in the future, since all the facts are not yet in and many of the conclusions and concepts will need more documentation.

Received for publication Sept 20, 1969; accepted Oct 8.

From the Department of Nutrition, Harvard School of Public Health, Boston.

Reprint requests to 665 Huntington Ave, Boston 02115 (Dr. Seltzer).

A convenient starting point is the *Surgeon General's Advisory Committee's Report* of 1964. After considering all the available information on smoking and CHD, the committee concluded that "male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance."[1] However, since 1964 there has accumulated a considerable body of data bearing on this area of concern, and it is from this additional evidence that we can best judge where we now stand on the effect of smoking on CHD. Epidemiological, pathological, experimental, and clinical evidence will be examined in turn.

Epidemiological Evidence

Recently, I reviewed the new epidemiological evidence.[2] The conclusion of the Surgeon General's 1964 report that male cigarette smokers have a higher death rate from CHD than men who do not smoke has been confirmed in the new studies published since the report was issued. Prospective studies of smoking and death rate gave a median mortality ratio (current cigarette smokers to nonsmokers) of 1.7, with no appreciable excess in deaths among cigar and pipe smokers. Angina pectoris, which represents about 20% of all manifestations of CHD, was fo

the most part found to be unrelated to cigarette smoking. Significantly, duration of cigarette smoking was found to be unassociated with excess CHD mortality, and conflicting results were obtained with regard to the effect of cigarette smoke inhalation. There also were a number of inconsistencies and inversions in reports of a consistent, rising gradient of CHD mortality with increasing amounts of cigarettes smoked. Those who smoked the most cigarettes had higher CHD rates than those who smoked the least, but the disease rates of the those smoking intermediate amounts were almost invariably the same or lower than those of those who smoked the least. The data dealing with discontinuance of smoking gave contractory and inconsistent findings and reflected on the problem of drawing valid conclusions from such data in exsmokers. In sum, collateral epidemiological evidence related to reasonable mechanisms was found to be weak, negative, or nonsupportive.

This in no way obviates the basic observation that cigarette smokers show excess mortality and disability from CHD, including sudden death. This observation still stands and commands attention and explanation. It means that the collateral epidemiological evidence is not supportive with respect to CHD as similar evidence is for smoking and other diseases, such as lung cancer and chronic bronchitis.

Pathological Evidence

It has been hypothesized that cigarette smoking has a long-term effect on CHD through a cumulative process of augmentation of atherogenesis.[3] The studies of Auerback et al[5] and Strong et al[6] in hospital autopsy cases found advanced degrees of atherosclerosis to be higher among cigarette smokers than among nonsmokers and increased with amount of smoking.

In more recent studies of populations likely to be less selected for arterial disease or smoking habit, Viel and associates[8] found "no relationship between atherosclerotic lesions and the use of tobacco" in an autopsy study of violent deaths (ages 10 to 70 years). In another study of violent deaths among consecutive accident victims (ages 16 to 49 years) Benson and Galindo (written communication, Jan 1968) found no significant differences in amount and type of atherosclerosis between smokers and nonsmokers. As noted by W. Kannel, MD (oral communication, August 1969), the autopsy series of the Framingham Study shows no correlation of degree of uncomplicated coronary artery atherosclerosis and the antecedent premorbid cigarette smoking habit.

That cigarette smoking has a chronic or cumulative effect leading to advanced degrees of atherogenesis is, also, inconsistent with several established observations: that duration of cigarette smoking is not associated with excess deaths from CHD,[7-9] with the lack of uniform evidence of an association of cigarette smoking with angina pectoris, and with the decreased statistical association of cigarette smoking and CHD in older subjects. The evidence, then, for a long-term effect of cigarette smoking contributing to excess CHD through a process of augmentation of atherosclerosis is not clear-cut, and is inconsistent with other pertinent information.

Clinical and Experimental Evidence

This section deals with the acute effects of cigarette smoking. These effects rather than the possible long-term effects of smoking are the present major basis of suspicion of harm to the cardiovascular system.[10] Of the various components of tobacco smoke with acute pharmacologic effects, the focus until recently was almost exclusively on nicotine. Lately, other constituents of tobacco smoke, principally carbon monoxide, have also been receiving attention.

Much is known concerning the acute cardiovascular effects of nicotine in man and experimental animals. In low concentrations, nicotine stimulates the sympathetic and parasympathetic ganglia, and in high concentrations, paralyses them. Thus, nicotine can cause liberation of catecholamines from the adrenal medulla. Nicotine can also have a sympathomimetic effect by causing the discharge of epinephrine and norepinephrine from chromaffin cells in various tissues, and in addition, can produce effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. The net results are transient, noncumulative, reversi-

ble increases in heart rate; cardiac output, ie, cardiac work; systolic blood pressure; and in rate and depth of breathing.

The Surgeon General's 1964 committee reviewed and analyzed the large body of data available to them on the acute effects of cigarette smoking and found "no unique cardiovascular effects" were demonstrated to "seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease."[1] The conclusions were based on the effects of nicotine; carbon monoxide was not considered.

Since then there has accumulated a considerable amount of additional experimental material. These data have led the Public Health Service to advance the theoretical concept of mechanisms, whereby ". . . in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may 'trigger' myocardial oxygen deficits of critical degree" leading to myocardial infarction and sudden death.[10]

Let us examine the more important of these mechanisms. This can be done best by posing a number of questions and attempting to answer them on the basis of the present evidence.

1. Does cigarette smoking "trigger" or "contribute to" increased incidence of acute myocardial infarction or sudden death through critical reductions in coronary nutrient capillary blood flow? The evidence that it could rests on the observations that cigarette smoking creates increased myocardial oxygen demands owing to the nicotine-induced catecholamine effect, and that while in normal persons the response is a compensatory increase in coronary blood flow, in some CHD patients, the compensatory increase in blood flow is absent.[11] The problem then rests on how critical is the absence of compensatory increase in coronary blood flow in persons with already impaired coronary circulation, in the light of differences in amount and frequency of smoking, of the condition and activity level of the patient, and considering that the effects of smoking are transient and noncumulative. The evidence on these points is not yet available; the question is challenging and remains to be answered.

2. Does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree through "the impairment of coronary blood as a result of the increased blood viscosity associated with hyperlipemia and hemoconcentration"[10] It has been reported that hemoconcentration occurs both in cigarette smokers and in patients with myocardial infarction, and that increased fatty acids increase the force necessary to "shear" blood. However, conflicting results have been obtained with respect to hemoconcentration in persons with CHD.[12,13] The concepts of viscosity of blood as influenced by rate of shear and hematocrit value are presently, as Burch and DePasquale[14] point out, "highly speculative." The whole question is exceedingly complex. There are no data directly relating smoking to fatal CHD events through measurable increased blood viscosity in patients with CHD. This interesting concept is still hypothetical and without documentation.

3. Does cigarette smoking, by a catecholamine effect, "trigger" myocardial oxygen deficit of a critical degree through "the increase of myocardial wall tension and velocity of contraction?"[10] That nicotine or cigarette smoking or both, augment heart muscle contractility and consequently increase myocardial oxygen need, is consistent with the evidence. The extent of the increase in oxygen demand, however, is imperfectly known and dependent on factors involved in the complexity of myocardial energetics and nicotine absorption. Where, when, in what circumstances are the levels of oxygen requirements occasioned by increased myocardial contractility not met? The answer to the question is still to come.

4. Does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree "through a predisposition to acute arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release?"[10] Support for this hypothesis comes, in part, from experimental studies in dogs in which direct administration of nicotine induced varying effects on the complicated neural and humoral mechanisms affect heart rate and rhythm, and an enhancement of Purkinj fiber "automaticity."[15,16] Webb et al showed, following bipolar ventricular electrode stimulation of dogs, a postresponse to cigarette smoking in which hemodynamic

changes quickly returned to normal, and the fibrillation threshold declined slowly and eventually fell below threshold baseline. As far as studies in humans are concerned, there appear to be no hard facts on this subject, no conclusive evidence that cigarette smoking precipitates "serious, life-threatening arrhythmias." But since arrhythmias can lead to clinical disability and death it is important that this subject be thoroughly investigated.

5. Does cigarette smoking lead to thrombus formation? In the presence of impaired coronary artery circulation, does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree through an increase in platelet adhesiveness?

Helpful reviews of the literature on smoking and thrombosis have been provided by Murphy and Mustard[18,19] and again most recently by Murphy.[20] These authors find no satisfactory answer to the question, "Does smoking lead to thrombus formation?" They note that the experimental approach with laboratory animals is replete with difficulties in simulating human cigarette smoking, and that the assessment of thrombosis is a problem since the techniques used do not represent thrombosis but clotting of shed blood. The problem of microthrombi is even more difficult.

Murphy and Mustard note that actual experimental work in connection with smoking and thrombus formation is scanty, and consider inconclusive the results of Engelberg and Futterman,[22] who used the Chandler loop, in which a significant reduction in thrombus formation time was reported in some subjects after they smoked two cigarettes. In answer to the question, "Which constituents in tobacco smoke are producing the effect?" Murphy and Mustard state that there is "embarrasingly little information" and no formal conclusions can be drawn. They note that the evidence at present is circumstantial while they indicate that "nicotine may be responsible." After consideration of the studies relating the platelet, arterial wall, coagulation, and fibrinolysis to thrombogenesis, the reviewers conclude:

> The evidence, so far, suggests the tentative conclusion that smoking is associated with a transient increase in tendency to form thrombi and this result could be largely explained by the release of endogeneous epinephrine by absorbed nicotine.

Studies of Spain et al[21] and Engelberg and Futterman[22] do ntt support the suggestion that cigarette smoking may precipitate acute coronary artery events by altering the blood coagulability as a result of stimulation to catecholamine production and free fatty acid mobilization.

Because of the difficulty of studying thrombus formation in man, special emphasis has been placed on blood coagulation, even though coagulation and thrombus formation are not identical. In studying possible smoking effects on thrombus formation in man, observers have relied heavily on in vitro phenomena with the attendant problems of experimental control and of transposing in vitro results to intact man. It is possible that clotting may be the least important mechanism in the thrombotic development, and that thrombosis will only occur when vessel damage is present and when there is decreased flow through vasoconstriction.

At the present state of our knowledge, it is possible that release of endogeneous epinephrine through nicotine absorption may produce transient increases in platelet aggregation in some persons. But this evidence is confounded with factors inherent in the nature of the experiments and in man's great variation and unique homeostatic propensities. Even if experimental methods and design were adequate, the question of smoking and thrombus formation would still remain an extremely difficult problem. From the evidence now available, no firm conclusion is possible that cigarette smoking so affects the thrombus forming process in human blood as to account for a portion of the excess deaths from CHD that occur in cigarette smokers.

6. Does the carbon monoxide constituent of cigarette smoke result in or contribute to increased myocardial infarction or sudden death either in normal individuals or in persons with already impaired coronary circulation due to CHD?

Studies have shown that the carbon monoxide constituent of cigarette smoke does effect increases (2% to 10%) in the levels of carboxyhemoglobin (COHb) saturation when heavy cigarette smokers and nonsmok-

ers were compared, with the consequent displacement of oxyhemoglobin. In addition, carbon monoxide effects a shift to the left of the oxygen-hemoglobin dissociation curve, which may result in a decreased release of oxygen at the tissue level.[23]

On the whole, experimental and clinical investigations bearing on this question are few. The most salient work in this area has been performed by Ayres and associates.[24] In 26 human subjects before and after carbon monoxide inhalation, these investigators found no significant change in oxygen tension. In another experiment, after exposure to carbon monoxide, coronary blood flow increased significantly in seven non-CHD patients but not in four patients with arteriographically proven CHD. In the patients with CHD, myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting anaerobic metabolism.

If carbon monoxide does in fact appreciably decrease oxygen extraction at the myocardial level, the matter of oxygen consumption may hinge on the extent of increase in coronary blood flow in normal persons, while in persons with diseased coronary arteries, the increase in blood flow is slight or absent. Hence, it may be a question of the ultimate balance of these opposing forces. In normal persons, there is the presumption that the increased coronary blood flow more than matches the presumed decrease in oxygen extraction. Whether or not this fails to occur in patients with obvious CHD, to such an extent as to "trigger" a coronary event is as yet unknown and much work remains to be done in this area.

Summary

Where do we now stand? Certain facts are clear. It is clear that there is a higher mortality rate from cardiovascular disease in cigarette smokers than in nonsmokers. The epidemiological evidence about duration of smoking, inhalation, amount of smoking, and stopping smoking has been shown to be inconclusive or less supportive with respect to CHD than for smoking and other diseases. A chronic effect of cigarette smoking is not clear and is inconsistent with other information. As far as acute effects are concerned, a series of physiological mechanisms have been advanced whereby cigarette smoking could trigger myocardial oxygen deficits of a critical degree in the presence of impaired coronary circulation due to CHD. This hypothesis has not been reasonably substantiated. Some of the evidence is provocative, but in many instances the hypothesized mechanisms are inadequately documented or not documented at all.

The statistical association of higher mortality from CHD in cigarette smokers still remains to be explained. An explanation may lie in a constitutional and genetic predisposition both to cigarette smoking and CHD. A genetic factor in the etiology of CHD is well accepted, and there is a growing body of evidence that smokers are different from nonsmokers in a large variety of biological ways and behavioral patterns, including "style of life."[25,26] If smokers show a greater tendency toward heart disease than nonsmokers because they are different kinds of people than nonsmokers—more vulnerable constitutional types—this could explain the comparatively low degree of association (mortality ratio of 1.7) of excess heart disease among cigarette smokers. At present, this has not been fully established. More research in this area is vitally necessary.

The *Surgeon General's Advisory Committee's Report* on "Smoking and Health" concluded in 1964 that "male cigarette smokers have a higher death rate from coronary heart disease than nonsmoking males, but it is not clear that the association has causal significance."[1] I believe this is where we still stand.

We are mindful that absolute proof is unattainable. We are also mindful, however, of the hazards of inadequate knowledge. More work must be done and new information gathered until the crucial questions are illuminated.

Assuredly, this opinion cannot be satisfying to those readers who are seeking a yes and no answer to the question whether or not cigarette smoking carries a serious risk of CHD. Fair-minded persons will concede that this opinion is mainly due to the unsatisfactory state of the evidence, which only time and more intensive study will resolve.

This investigation was supported by the Fund for Research and Teaching of the Department of Nutrition, Harvard School of Public Health, Boston.

References

1. "Smoking and Health," in *Report of the Advisory Committee to the Surgeon General*, US Dept of Health, Education and Welfare, Public Health Service, 1964.

2. Seltzer, C.C.: An Evaluation of the Effect of Smoking on Coronary Heart Disease: I. Epidemiological Evidence, *JAMA* 203:193-200 (Jan 15) 1968.

3. *The Health Consequences of Smoking*, suppl, publication 1696, Public Health Service, 1967.

4. Auerbach, O.; Hammond, E.C.; and Garfinkel, L.: Smoking in Relation to Atherosclerosis of the Coronary Arteries, *New Eng J Med* 273:775-779 (Oct) 1965.

5. Strong, J.P., et al: Relationship Between Cigarette Smoking Habits and Coronary Atherosclerosis Heart Disease, abstracted, *Circulation*, 34(suppl 3):31, 1966.

6. Viel, B.; Donoso, S.; and Salcedo, D.: Coronary Atherosclerosis in Persons Dying Violently, *Arch Intern Med* 122:97-103 (Aug) 1968.

7. Doyle, J.T., et al: The Relationship of Cigarette Smoking to Coronary Heart Disease: The Second Report of the Combined Experience of the Albany, NY, and Framingham, Mass, Studies, *JAMA* 190:886-890 (Dec 7) 1964.

8. Kahn, H.A.: "The Dom Study of Smoking and Mortality Among US Veterans: Report on 8½ Years of Observation, *Nat Cancer Inst Monog* 19:1-125 (Jan) 1966.

9. Best, E.W.R., et al: Summary of a Canadian Study of Smoking and Health, *Canad Med Assoc J* 96:1104-1108 (April) 1967.

10. *The Health Consequences of Smoking*, supplement, Public Health Service publication 1696, Public Health Service, 1968.

11. Bing, R.J.; Cohen, A.; and Bluemchen, G.: "Tobacco Alkaloids and Circulation," in *Tobacco Alkaloids and Related Compounds, Proceedings of the fourth International Symposium, Wenner-Gren Center, Stockholm, February 1961*, New York: Pergamon Press, Inc., 1965, p 211.

12. Conley, C.L., et al: Hematocrit Values in Coronary Artery Disease, *Arch Intern Med* 113:170-176 (Feb) 1964.

13. Mc Donough, J.R., et al: The Relationship of Hematocrit to Cardiovascular States of Health in the Negro and White Populations of Evans County, Georgia, *J Chron Dis* 18:243-257, 1965.

14. Burch, G.E., and DePasquale, N.P.: The Hematocrit in Patients With Myocardial Infarction, *JAMA* 180:63-65 (April 7) 1962.

15. Nadeau, R.A., and James, T.N.: Effects of Nicotine on Heart Rate Studies by Direct Perfusion of Sinus Node, *Amer J Physiol* 212:911-916 (April) 1967.

16. Greenspan, K.; Knoebel, S.B.; and Fisch, C.: Effect of Nicotine Upon Human and Canine Cardiac Action Potential and Contractile State, abstracted, *Project for Research on Tobacco and Health 1964-1968: Report to the Profession and Abstracts of Grants*, Chicago, AMA-ERF, June 1968, p 24.

17. Webb, W.R.; Wax, S.D.; and Sugg, W.L.: Cigarette Smoke and Fibrillation Threshold in Dogs, abstracted, *Clin Res* 16:74 (Jan) 1968.

18. Murphy, E.A., and Mustard, J.F.: Tobacco and Thrombosis, *Amer J Public Health* 56:1061-1073 (July) 1966.

19. Murphy, E.A., and Mustard, J.F.: Smoking and Thrombosis, *Nat Cancer Inst Monogr* 28:47-55 (June) 1968.

20. Murphy, E.A.: "Thrombozyten, Thrombose und Gerinnung," in H. Shievelbein (ed.): *Nikotin, Pharmakologie und Toxikologie des Tabakrauches*, Stuttgart, Germany: Georg Thieme Verlag, 1968, pp 139-154.

21. Spain, D.M., et al: Sudden Death Due to Coronary Atherosclerotic Heart Disease: Age, Smoking Habits, and Recent Thrombi, *JAMA* 207:1347-1349 (Feb 17) 1969.

22. Engelberg, H., and Futterman, M.: Cigarette Smoking and Thrombotic Coagulation of Human Blood, *Arch Environ Health* 11:266-270 (Feb) 1967.

23. Astrup, P., et al: The Effect of Tobacco Smoking on the Dissociation Curve of Oxyhemoglobin, *Scand J Clin Lab Invest* 18:450-457, 1966.

24. Ayres, S.M., et al: Systemic and Myocardial hemodynamic Responses to Relatively Small Concentrations of Carboxhemoglobin (COHB), *Arch Environ Health* 18:699-709 (April) 1969.

25. Seltzer, C.C.: Constitution and Heredity in Relation to Tobacco Smoking, *Ann NY Acad Sci* 142:322-339 (March) 1967.

26. Thomas, C.B.: On Cigarette Smoking, Coronary Heart Disease, and the Genetic Hypothesis, *Johns Hopkins Med J* 122:69-76, 1968.

The mechanism by which cigarette smoke and hence nicotine induces these changes has been of interest to numerous investigators. Nicotine has long been known as a stimulator of both sympathetic and parasympathetic ganglia. Research has centered, therefore, on the function of catecholamines, mainly epinephrine and norepinephrine, as mediators, of these responses. Using isolated rabbit atrial myocardium, Burn and Rand (*35*) noted that the prior administration of reserpine to the perfusate blocked the increased rate and amplitude of contraction seen following the administration of nicotine. West, et al. (*208*) showed that the *in vivo* cardiac stimulating effect of nicotine was blocked by tetraethylammonium chloride. Leaders and Long (*125*), Romero and Talesnik (*156*), and, more recently, Ross and Blesa (*160*) have all demonstrated this blockade in animals using agents such as pentolinium, hexamethonium, guanethidine, and reserpine.

More direct evidence of the catecholamine-releasing effect of nicotine has been found by Watts (*202*) and Westfall, et al. (*209, 210, 211*) (table A22). Among animal subjects, nicotine administration and the inhalation of the smoke of standard cigarettes caused significant increases in peripheral arterial epinephrine levels, while cornsilk cigarette smoke inhalation evoked no such change. In humans, cigarette smoking was found to be associated with a significant increase in urinary epinephrine excretion.

The source of these nicotine-released catecholamines, particularly those which mediate the immediate and local cardiac responses to intracoronary injections of nicotine, is felt to be the myocardial chromaffin tissue (*35, 160*). The more widespread effects are most probably mediated by hormones released from the adrenal gland.

According to recent research of Saphir and Rapaport, catecholamine release may not be the sole mediator of these responses (*166*). These investigators reported that intra-arterial injections of nicotine into the mesenteric circulation of cats were followed within 1 to 2 seconds by enhanced myocardial performance, increased left ventricular systolic pressure, and increased systemic resistance. Sectioning of the mesenteric afferent nerves led to a diminished response. The authors concluded that the cardiovascular response to nicotine may also be neurogenic in nature. Nadeau and James (*142*) injected nicotine directly into the sinus node artery of dogs and noted an initial bradycardia, due probably to direct vagal stimulation, followed by tachycardia, due probably to catecholamine release.

That the presence of nicotine may predispose the myocardium, particularly a hypoxic or previously damaged myocardium, to arrhythmia formation is suggested by the research of Balazs, et al. (*16*), Bellet, et al. (*21*), and Greenspan, et al. (*74*). Balazs produced myocardial lesions in dogs either by pretreatment with isoproterenol or ligation of the anterior descending coronary artery. It was found that while normal animals did not develop arrhythmias upon challenge with small doses of intravenous nicotine, some animals with damaged myocardiums responded with increased arrhythmia formation shortly after their spontaneous arrhythmias had ceased. More recently, Bellet, et al. (*20*) studied the effect of cigarette smoke inhalation on the ventricular fibrillation threshold in anesthetized dogs. They observed a statistically significant decrease in the threshold following smoke inhalation. Greenspan, et al. (*74*), using isolated dog right ventricular myocardium, observed that nicotine perfusion increased the automaticity of the Purkinje fibers system and decreased the conduction velocity. The authors consider that these two nicotine-induced effects probably predispose the myocardium to the initiation of arrhythmias.

(*118*) Kiem, G. A., Sherrod, T. R. Action of nicotine and smoking on coronary circulation and myocardial oxygen utilization. Annals of the New York Academy of Sciences 90(1): 161–173, September 27, 1960.

(*35*) Burn, J. H., Rand, M. J. Action of nicotine on the heart. British Medical Journal 1: 137–139, January 18, 1958.

(*208*) West, J. W., Guzman, S. V., Bellet, S. Cardiac effects of intracoronary arterial injections of nicotine. Circulation Research 6: 389–395, May 1958.

(*125*) Leaders, F. E., Long, J. P. Action of nicotine on coronary vascular resistance in dogs. American Journal of Physiology 203(4): 621–625, October 1962.

(*156*) Romero, T., Talesnik, J. Influence of nicotine on the coronary circulation of the isolated heart of the cat. Journal of Pharmacy and Pharmacology 19(5): 322–323, 1967.

(*160*) Ross, G., Blesa, M. I. The effect of nicotine on the coronary circulation of dogs. American Heart Journal 79(1): 96–102, January 1970.

(*202*) Watts, D. T. The effect of nicotine and smoking on the secretion of epinephrine. Annals of the New York Academy of Sciences 90(1): 74–80, September 27, 1960.

(*209*) Westfall, T. C., Cipolloni, P. B., Edmundowicz, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine 123: 174–179, 1966.

(*210*) Westfall, T. C., Watts, D. T. Effect of cigarette smoke on epinephrine secretion in the dog. Proceedings of the Society for Experimental Biology and Medicine 112(4): 843–847, April 1963.

(*211*) Westfall, T. C., Watts, D. T. Catecholamine excretion in smokers and nonsmokers. Journal of Applied Physiology 19(1): 40–42, January 1964.

(*166*) Saphir, R., Rapaport, E. Cardiovascular responses of the cat to mesenteric intra-arterial administration of nicotine, cyanide and venous blood. Circulation Research 25(6): 713–724, December 1969.

(*142*) Nadeau, R. A., James, T. N. Effects of nicotine on heart rate studied by direct perfusion of sinus node. American Journal of Physiology 212(4): 911–916, April 1967.

(*16*) Balazs, T., Ohtake, S., Cummings, J. R., Noble, J. F. Ventricular extrasystoles induced by epinephrine, nicotine, ethanol, and vasopressin in dogs with myocardial lesions. Toxicology and Applied Pharmacology 15(1): 189–205, July 1969.

(*21*) Bellet, S., Kershbaum, A., Meade, R. H., Jr., Schwartz, L. The effect of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. American Journal of the Medical Sciences 201(1): 40–51, January 1941.

(*74*) Greenspan, K., Edmands, R. E., Knoebel, S. B., Fisch, C. Some effects of nicotine on cardiac automaticity, conduction, and inotropy. Archives of Internal Medicine 123(6): 707–712, June 1969.

(*20*) Bellet, S., Fischmann, D., Roman, L., Deguzman, N. The effect of cigarette smoke inhalation on the ventricular fibrillation threshold. Circulation (Supplement 3) 42(4): 135, October 1970.

Source of Catecholamines. Since (35) Burns and Rand and (160) Rose and Blasa used either the isolated heart or the intact heart with intracoronary injection of nicotine, the source of catecholamines will have to be from the heart. However, with inhalation of cigarette smoke, the more important source is adrenal gland which was demonstrated by (210) Westfall and Watts. Portions of this article are reproduced below.

The site of release is an important point for the thesis appearing in the document. A cardiac source would mean high level of catecholamines whereas an adrenal source would mean low level of amines reaching the heart.

Discussion. These results show that inhalation of cigarette smoke can cause a significant increase in secretion of epinephrine from the adrenal gland of the dog. It is well established that nicotine is the chief pharmacologically active substance in cigarette smoke (16,17). Nicotine in large doses can cause the release of catecholamines from the adrenal gland(2,3,4). Control experiments involving no smoking and the smoking of cornsilk cigarettes had no effect on epinephrine secretion. The effect of asphyxia and hypoxia was very small when compared to cigarette smoking. The data indicate it is the nicotine in the smoke which produced the observed responses.

It is apparent that the increase in epinephrine content during smoking is greatest in the vena cava blood, followed by the arterial and peripheral venous blood, respectively. The vena cava blood contains the immediate secretions from the adrenal glands diluted by blood flow from the posterior part of the body only. By the time the secretions from the adrenal glands reach peripheral arterial blood, the epinephrine has been further diluted by the total venous return and possibly by inactivation in the lungs. Finally, epinephrine content is further decreased by passage through the tissues of the hind leg so the lowest concentration appears in the peripheral venous blood. Further significance is placed on the fact that inhalation of cigarette smoke produced an increase in epinephrine levels of peripheral arterial blood since this is the blood which reaches all tissues. To simulate more closely cigarette smoking in humans, experiments were carried out in which inhalation of cigarette smoke was controlled at a slow rate. Smoking time in these experiments was 8 minutes which is comparable to the average human cigarette smoking time. The results show that from control levels of less than 1 μg l the slow inhalation of cigarette smoke increased epinephrine levels of peripheral arterial blood to 25.1 μg l ($p<0.001$). This elevation in epinephrine levels was found to increase progressively to a maximum value during the smoking period. In the previous experiments, where average smoking time was 3.5 minutes, inhalation of cigarette smoke caused an increase in arterial epinephrine level from an undetectable amount before the cigarette to a value of 126 μg l during the cigarette. Although consideration must be given to species and weight differences, these results indicate that a similar effect can occur in man during cigarette smoking.

Results obtained in this study on the differential release of epinephrine and norepinephrine are in agreement with results reported in the literature on release of epinephrine and norepinephrine by nicotine(10-14) in that the increase of catecholamines in the peripheral circulation is due primarily to a release of epinephrine from the adrenal medulla.